A TEXTBOOK OF MEDICINE

BY AMERICAN AUTHORS

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PREFACE TO THE SIXTH EDITION

The Sixth Edition of the Textbook of *Medicine by American Authors* makes its appearance with extensive changes in both text and format For example, it contains a number of new articles on subjects not covered in previous editions

Virus Pneumonia	Dr Russell L Cecil
Salmonella Suipestifer Infection	Dr Charles A Janeway
Friedlander s Bacillus Infections	Dr Maxwell Finland
Hirudinea	Dr Ernest Carroll Faust
Contact Dermatitis	Dr Harry L Alexander
Aviation Medicine	Dr Alvan L Barach
Seasickness and Air Sickness	Dr Alvan L Barach
Undernutrition	Dr Cyril M MacBryde
Pathologic Physiology of Circulatory Failure and Cardiac Pain	Dr Eugene A Stead Jr
Circulatory Collapse and Shock	Dr Eugene A Stead Jr
Rheumatic Heart Disease	Dr Clarence E de la Chappelle
Senile Osteoporosis	Dr Walter Bauer
Treatment of Infections with Penicillin	Drs Donald G Anderson and Chester S Keefer

In addition to these new topics the present edition contains the following new treatises *on subjects previously covered*

Measles	Dr Charles F McKhann
Varicella	Dr Joseph Stokes Jr
Smallpox	Dr Joseph Stokes Jr
Vaccinia	Dr Joseph Stokes Jr
Poliomyelitis	Dr John R Paul
Erysipelas	Dr Henry M Dawson
Septicemia	Dr Chester Scott Keefer
Focal Infection	Dr Russell L Cecil
Tetanus	Dr Warfield M Firor
Bacillus Coli Infection	Dr Charles A Janeway
Tularemia	Dr Karl F Meyer
Haverhill Fever	Dr W J Stainsby
The Mycoses	Dr David T Smith
Relapsing Fever	Brig Gen James Stevens Simmons A U.S
Weil s Disease	Dr W Barry Wood Jr
Diseases due to Animal Parasites	Dr Ernest Carroll Faust
Sarcoidosis	Dr William S Middleton
Milk Sickness	Dr Russell L Cecil
Miliary Fever	Dr Russell L Cecil
Opium Intoxication	Dr Lawrence Kolb
Cocaine Intoxication	Dr Lawrence Kolb
Diseases of the Intestines	Dr Walter L Palmer
Appendicitis	Dr I S Ravdin
Intestinal Obstruction	Drs Alton Ochsner and Michael E DeBakey
Intestinal Neoplasms	Drs Alton Ochsner and Michael E DeBakey
Affections of the Mesentery	Drs Alton Ochsner and Michael E DeBakey
Cardiac Arrhythmias	Dr Harold J Stewart
Diseases of the Motor Tracts	Dr Samuel B *Hadden*
Paralysis Agitans	Dr D Denny Brown
Convulsive States	Dr William G Lennox
Mental Disorders	Dr John C Whitehorn

Short introductory chapters have been added to most of the larger sections of the book It is hoped that these introductions will prove of value as condensed statements of the general physiologic principles underlying the diseases included in the section The following introductory chapters appear for the first time in this edition

Introduction to the Rickettsial Diseases	Dr S B Wolbach
Introduction to Pneumococcal Infections	Dr Russell L Cecil
Introduction to Deficiency Diseases	Dr John B Youmans
Introduction to Diseases of Metabolism	Dr William T Salter
Introduction to Diseases of the Digestive System	Dr Walter L Palmer
Introduction to Diseases of the Blood	Dr W B Castle
Introduction to Diseases of the Cardiovascular System	Dr Robert L Levy
Introduction to Diseases of the Ductless Glands	Dr Fuller Albright

Another new feature of the book which will be appreciated by all students and practitioners of medicine is a list prepared by Dr Ralph G Stillman of normal values for the commoner laboratory tests With the great multiplicity of tests now in use it becomes more and more difficult to keep normal values in mind For the convenience of the reader Dr Stillman's contribution has been placed at the end of the book immediately preceding the section on treatment of infections with penicillin

In the present edition particular attention has been given to the section on Diseases of the Cardiovascular System The material has been rearranged and several new chapters have been added The editor is grateful to Dr Robert L Levy for valuable suggestions in connection with this section and for discriminating editorial work on the galleys

Because of present day interest in tropical medicine the idea of grouping all tropical diseases together in one section of the book was seriously considered However after further consideration it seemed wiser for teaching purposes to retain the present etiological arrangement

In the Fifth Edition the editor for the first time introduced illustrations into the text This innovation has proved so popular that the number of illustrations in the present edition has been increased

In the Sixth Edition the text has been rearranged in double columns a format which should add greatly to the convenience and comfort of the reader While the page itself has been only slightly enlarged the thickness of the book has been greatly reduced thereby The editor hopes that these changes will be acceptable to teachers students and practitioners who make frequent use of the book

It is a matter of deep regret to have to report the death of eleven contributors Dr Kenneth D Blackfan Dr C Macfie Campbell Dr Raymond L Ditmars Dr Walter W Hamburger Dr Dean Lewis Dr Frederick T Lord Dr A Graeme Mitchell Dr Walter L Niles Dr Joe Harold St John Dr Andrew Watson Sellards and Dr Soma Weiss The editor greatly laments the passing of these distinguished physicians who by their zealous cooperation have contributed so much to the success of the book

In planning the Sixth Edition the editor invited Dr Soma Weiss late Hersey Professor of the Theory and Practice of Physic at Harvard University to act as co editor During the short time of his service Dr Weiss contributed many valuable suggestions and criticisms and his untimely death was a grievous loss to the editor and publishers

The editor is very happy to announce that the present edition of the Textbook is being translated into Spanish and Portuguese The translations should be in print shortly after the appearance of the new edition in English

The preparation of what might be called a war time edition of the Textbook has been no easy task Many contributors are in the service of the Army and Navy and dispersed over the United States and various foreign countries One revised article came all the

was from Chengtu China The overworked professors of medicine who have remained on duty at home must have found it more difficult than ever to prepare adequate revisions of their manuscripts Many thanks to all for such splendid cooperation!

Special acknowledgments are due to Dr Alice Childs and Mrs Natalie J Hoyt for their assistance in proof reading and general editorial work

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CONTENTS

THE INFECTIOUS DISEASES

VIRUS DISEASES

PAGE

THE RICKETTSIAL DISEASES

THE BACTERIAL DISEASES

PNEUMOCOCCAL INFECTIONS

STREPTOCOCCAL INFECTIONS

STAPHYLOCOCCAL INFECTIONS

PAGE

GONOCOCCAL INFECTIONS

MENINGOCOCCAL INFECTIONS

BACILLARY INFECTIONS

THE MYCOSES

SPIROCHETAL INFECTIONS

PROTOZOAN INFECTIONS

METAZOAN INFECTIONS

THE PLATYHELMINTHES

THE NEMATHELMINTHES

HIRUDINEA

ARTHROPODS AND HUMAN DISEASE

DISEASES OF DOUBTFUL OR UNKNOWN ORIGIN

DISEASES OF ALLERGY

DISEASES DUE TO PHYSICAL AGENTS

DISEASES DUE TO CHEMICAL AGENTS

THE INTOXICATIONS

DEFICIENCY DISEASES

DISEASES OF METABOLISM

DISEASES OF THE DIGESTIVE SYSTEM

DISEASES OF THE STOMACH

DISEASES OF THE INTESTINES

DISEASES OF THE LIVER

DISEASES OF THE PANCREAS

DISEASES OF THE PERITONEUM

DISEASES OF THE RESPIRATORY SYSTEM

DISEASES OF THE NOSE

DISEASES OF THE LARYNX

DISEASES OF THE BRONCHI

DISEASES OF THE LUNGS

DISEASES OF THE PLEURA

DISEASES OF THE MEDIASTINUM

DISEASES OF THE DIAPHRAGM

DISEASES OF THE KIDNEYS

DISEASES OF THE SPLEEN AND RETICULO-ENDOTHELIAL SYSTEM

DISEASES OF THE SPLEEN

DISEASES OF THE RETICULO ENDOTHELIAL SYSTEM

DISEASES OF THE BLOOD

DISEASES OF THE CARDIOVASCULAR SYSTEM

DISEASES OF THE HEART

DISEASES OF THE ARTERIES

DISEASES OF THE PERIPHERAL VESSELS

DISEASES OF THE DUCTLESS GLANDS

DISEASES OF THE THYROID GLAND

DISEASES OF THE HYPOPHYSIS

DISEASES OF THE SUPRARENAL GLANDS

PAGE

DISEASES OF THE THYMUS GLAND

DISEASES OF THE PARATHYROID GLANDS

DISEASES OF THE PINEAL GLAND

DISEASES OF THE SEX GLANDS

DISEASES OF THE LOCOMOTOR SYSTEM

DISEASES OF THE MUSCLES

DISEASES OF THE JOINTS

DISEASES OF THE BONES

DISEASES OF THE NERVOUS SYSTEM

A TEXTBOOK OF MEDICINE

BY

AMERICAN AUTHORS

THE INFECTIOUS DISEASES*

VIRUS DISEASES

INTRODUCTION

INFECTIOUS diseases are caused by certain kinds of active agents or their toxins Such agents are divided into the following groups Protozoa fungi bacteria spirochetes rickettsiae and viruses The diseases of man that are known to be caused by or that are strongly suspected of being caused by viruses are measles German measles mumps fever blisters herpes zoster varicella smallpox, vaccinia rabies psittacosis common cold influenza, St Louis type of encephalitis Japanese type B encephalitis epidemic encephalitis equine encephalomyelitis epidemic pleurodynia lymphocytic choriomeningitis poliomyelitis lymphogranuloma inguinale Australian X disease louping ill Rift Valley fever foot and mouth disease yellow fever pappataci fever dengue fever, warts and molluscum contagiosum

The nature of viruses is not definitely known At present however three groups of ideas seem to cover the possibilities (1) The smallest viruses *e g* the viruses of foot and mouth disease and poliomyelitis may be inanimate incitants of disease transmissible in series Stanley believes that the virus of tobacco mosaic is a nucleoprotein and reports that he is able to obtain it regularly in crystalline form His work is significant and if his interpretations of it are accepted progress will have been made in regard to the nature of certain viruses (2) The medium sized viruses as exemplified by the etiologic agents of yellow fever and fever blisters may represent forms of life unfamiliar to us (3) The virus of vaccinia might well be a minute living autonomous organism or a midget in the microbial world provided the elementary bodies which are infectious and are composed of protein fats carbohydrates and ash represent nothing but individual units of the virus Regardless of the nature of viruses it is accepted that they are smaller than ordinary bacteria and that none of them has been cultivated in the absence of living cells Therefore dead or alive they may be considered as obligate parasites

That the viruses are exceedingly small and that they have not been shown capable of multiplication in the absence of living cells are not sufficient reasons for considering the variety of diseases caused by them as possessing pathologic changes in common Indeed one is repeatedly asked Why are smallpox poliomyelitis mumps and warts diseases with exceedingly diverse clinical pictures grouped together? It is believed that viruses are intimately associated with the cells injured by them and that they multiply or are regenerated within such cells As a consequence of this intimate association viruses exert upon the tissues of their host a decided influence which results in hyperplasia or necrosis In the past pathologists devoted most of their attention to inclusion bodies and inflammation and considered them of prime importance in virus diseases Inclusion bodies are of great significance but they do not occur in all virus diseases Inflammation is seen in most virus maladies but it is nothing more than a secondary phenomenon appearing in the wake of cellular destruction While inclusions are important and inflammation regularly occurs in virus maladies hyperplasia hyperplasia accompanied by necrosis and

* See pages 1532–1536 Treatment of Infections with Penicillin

necrosis the primary pathologic phenomena of virus diseases are common to all characterize them, and logically permit of their segregation, in spite of diverse clinical pictures into the same group of diseases

Most virus diseases are followed by a permanent immunity which is not the rule in bacterial maladies There are exceptions *e g* common colds and fever blisters While there is no general agreement regarding the cause of the lasting immunity many are inclined to believe that repeated contacts with certain viruses the intimate type of parasitism observed in virus maladies or the prolonged, possibly persistent sojourn of some viruses in infected hosts account for the phenomenon

As a rule once signs and symptoms of infection have become manifest specific serum therapy is of no value in virus diseases This is readily understandable in the light of the fact that viruses intracellularly situated are not affected by antibodies and that by the time signs of disease are obvious most, if not all of the susceptible cells that are going to be involved have already been entered

The etiologic agents of virus diseases are smaller than ordinary bacteria appear to be obligate parasites are intimately associated with the cells stimulated or destroyed by them frequently cause inclusion bodies in affected cells usually induce a lasting immunity, and are not harmed by antisera once they have become *intracellularly* situated In view of these facts viruses have been separated from other and better known infectious agents and to the initiate the term *virus* carries as much significance as does the word *bacterium* Consequently the expressions *virus of smallpox* and *Virus variolae* are just as specific in their designation as are the expressions *bacillus of typhoid* and *Bacillus typhosus*

THOMAS M RIVERS

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THE COMMON COLD

(*Acute Coryza*)

Definition —The common cold or acute coryza, is a catarrhal inflammation of the upper respiratory tract which results from infection by a filtrable virus or microorganisms, and perhaps from allergic and metabolic derangements not yet well understood Such terms as acute rhinitis 'acute pharyngitis acute laryngitis or tracheitis are often employed to designate the region chiefly affected by the disease

Etiology —The communicability of many catarrhal disorders of the upper respiratory tract indicates the presence of an infective agent but cultures of the nasopharyngeal secretions of patients with colds usually reveal organisms indistinguishable from those found in the nose and throat of healthy individuals The commonest of these are various strains of staphylococcus streptococcus pneumococcus *Micrococcus catarrhalis* and influenza bacillus It is improbable that any of these well known bacteria are the usual inciting agent of the common cold Frequently during the early stages of the disease micro organisms of all kinds are strikingly few and it is only after several days that one or more types of pathogens appear in large numbers in the exudate

In recent years it has been shown by numerous observers that in the nasal secretions of many persons suffering from a fresh cold there is an ultramicroscopic agent which when instilled into the nostrils of normal individuals reproduces the disease Dochez and his co workers have succeeded in cultivating this agent in embryonic tissue media and have indicated that it should be classified among the filtrable viruses Most colds occurring in epidemic form are probably caused by a virus or group of viruses

Following an initial injury of the epithelium bacteria transmitted with the virus or bacteria already present in the respiratory tract assume the role of secondary invaders and may give rise to further symptomatology Small outbreaks of colds are sometimes caused by micro-organisms capable of invading the healthy mucous membrane in the absence of a concurrent virus infection It is not unlikely that the mucus and nasopharyngeal secretions in which the causative agent of colds is disseminated are factors in the epidemiology of the disease for it has been shown that the presence of these materials lowers the natural resistance of the tissues to bacterial invasion

Unaccustomed exposure of the body to cold and the wearing of wet shoes and clothing often precipitate colds Observations made in isolated communities indicate however, that physical exposures and hardships do not *per se* induce coryza unless an agent of infection is also present It is well known that general immunity may be depressed when the body is subjected to sudden temperature changes Furthermore in man chilling of the skin brings about prompt vasomotor reactions in the nasopharynx accompanied usually by ischemia and cooling of the mucous membranes These changes are temporary in the normal subject but in persons prone to catching cold the reaction is said to be sluggish and prolonged It is assumed by most observers that there is a local injury of the tissues and disturbances in the nasal secretions during these episodes which promote infection by pathogenic agents present in the upper respiratory tract Irritants and specific antigens may act similarly but vasomotor disturbances may be induced not only by allergens in the air or food or injected vaccines but may represent a local reactivity in the nasopharynx to systemic derangements affecting vascular tone through physiologic imbalances in the vegetative nervous system Hence the factors of constitution fatigue and emotional strain may be of etiologic importance in certain instances

Many persons have structural abnormalities or foci of chronic infection in the upper respiratory tract such as hypertrophied adenoids nasal polyps or chronic sinusitis where pathogenic bacteria are harbored and normal drainage is disturbed Such persons are not only victims of epidemic coryza but also develop colds when local resistance is impaired by any of the factors mentioned above

Thus it may be seen that the common cold is probably not a clinical entity but comprises a group of different affections The epidemic form may result from primary bacterial invasion but in most instances is due to an ultramicroscopic agent Many are produced by environmental or constitutional factors which lower resistance and allow the common pathogens normally harbored in the upper respiratory tract to invade the mucous membranes

Morbid Anatomy —The characteristic lesion of the common cold is a catarrhal inflammation of any part of the upper respiratory tract or paranasal sinuses The process often begins at a focal area and spreads as the causative agent and irritating bacterial substances are disseminated through the network of lympathics beneath the epithelial surface The local reaction frequently stimulates a vasodilatory reflex which increases the engorgement of the spongy tissues of the nose

The mucous membrane is red and thickened and is covered by an excess of seromucoid secretion that becomes purulent in the later stages Microscopic examination shows little except hyperemia and edema of the tissues and, in the later stages of the inflammatory process an increase of wandering cells Necrosis and desquamation of the epithelial cells follow the initial inflammatory process

The systemic reactions that frequently accompany coryza result from absorption of toxic products from the diseased area

Epidemiology —Diseases of the upper respiratory tract are often highly communicable and may spread readily among the members of a locality Persons with fresh colds transmit the infection most readily At times however the disease seems limited to a single individual and is not contracted even by those in close contact with the patient Both epidemic and sporadic types are much more common during the colder months of the year They are especially numerous in the autumn late in September or during October in midwinter during Janu

ary and February, and again in the spring usually in April This seasonal variation does not depend entirely upon weather conditions as is popularly supposed for the periodicity and severity of colds have been found strikingly similar in various regions irrespective of climatic differences Perhaps the factor of greatest importance is the change to indoor crowding during the winter months especially in schools Under conditions such as these the virulence of infecting agents may be greatly enhanced as they are transferred rapidly from one nonimmune subject to another Infection, once established is spread by sneezing coughing expectoration and blowing the nose all conspicuous features of colds The incubation period of coryza is highly variable Symptoms appear within twelve to ninety six hours after exposure to a coryza of the infectious type Other varieties may be precipitated within a few hours after chilling

Immunity may persist for weeks or months following a coryza Persons complaining of frequent colds usually suffer reinfection from a chronic focus in the sinuses or tonsils

Symptoms —The onset of coryza is usually marked by sensations of burning or itching at the primary site of invasion This is generally in the posterior nares but may be in any portion of the upper respiratory tract In about 30 per cent of cases the inflammation remains localized but in many instances the nose pharynx larynx trachea and paranasal sinuses become involved

At the height of the disease patients are quite dejected and uncomfortable Often they complain of chilly sensations and vague aching in the back and extremities The conjunctivae are suffused the nasal mucosa is red and swollen the nostrils are partly or completely occluded and from them pours continuously a watery discharge which causes much sniffing and blowing of the nose Areas of excoriation appear at the nasal orifices and around the mouth Headache and dull pain in the face and back of the nose are common and are aggravated by the inspiration of air The senses of smell taste and hearing are often impaired The voice becomes husky and muffled marked hoarseness indicates laryngeal involvement The tongue is dry and coated Swallowing and opening the mouth may be painful or difficult Nonproductive coughing is often the most distressing symptom with tracheitis it is associated with a sensation of tightness and soreness behind the sternum The lymph nodes near the angles of the jaw and in the neck may be swollen and tender Constitutional symptoms usually appear early, and vary extremely in severity even during a single epidemic They are not in proportion to the extent or appearance of the lesion in the nasopharynx In severe infections prostration is striking Often there is an elevation of temperature (100°-102° F) Digestive disturbances such as constipation diarrhea anorexia abdominal cramps and nausea are not uncommon especially in some epidemics

The symptoms may last a few days or many months Relapses are especially common seven to twelve days after the initial attack Bronchial involvement and pyogenic infections of the sinuses and middle ears run a tedious course As recovery from the cold progresses congestion gradually diminishes and the secretions become scanty and more purulent During convalescence there may be weakness loss of weight nervousness and insomnia Arthralgia neuralgia and cutaneous hyperesthesia are often troublesome late manifestations

Diagnosis —Typical coryza offers a few diagnostic difficulties Certain specific diseases such as *measles diphtheria scarlet fever pertussis* and *typhoid fever* may be accompanied by catarrhal symptoms at the onset and are consequently mistaken for infections of the upper respiratory tract until more characteristic features develop

Grippe and influenza are closely allied to the common cold The terms are frequently loosely employed to indicate any upper respiratory infection accompanied by toxic symptoms In the same outbreak all gradations between grippe and a mild congestion of the nasopharynx can be observed Recent work indicates that epidemic influenza is caused by a specific virus pathogenic for ferrets and white mice Further studies are necessary to determine whether there is a relationship of this virus to that producing the common cold

A mild or aborted cold is easily confused with noninfectious hyperemia of the nasal

mucous membranes due to such causes as local irritants drugs allergic reactions and various vasomotor phenomena Even with a careful history definite diagnosis may be impossible

Prophylaxis —Measures to prevent colds are of various types The most effective perhaps is reducing to a minimum contact with crowds and infected individuals Strict *isolation* is obviously impossible except for invalids and very young children

The use of germicidal aerosols such as propylene glycol vapor for sterilizing the air of rooms where crowding is prevalent offers the possibility of eventually controlling respiratory infections Prophylaxis of this type is however still in the experimental stage

Spraying and *gargling* with antiseptics are usually ineffectual because it is impossible to free the mucous membranes of bacteria by this method *Irrigations* are of value only when abnormalities in the nose or throat impair the natural mechanisms of elimination In such cases only the blandest solutions should be employed

Vaccines are of limited value Controlled statistics indicate that volunteers inoculated subcutaneously with stock bacterial vaccine or given a polyvalent vaccine orally develop colds about as frequently as those receiving inert material For patients however who suffer from repeated reinfections because of a chronic focus in the respiratory tract vaccine therapy is rational The attempts to immunize against the virus causing coryzas have thus far been unsuccessful Usually infected *foci should be removed surgically* Children especially have fewer colds after *tonsillectomy* or *adenoidectomy*

Exposure to chilling and *out-of-door hardship* are sometimes recommended to increase resistance to respiratory diseases Fresh air minimizes the chance of infection but probably does not affect the susceptibility of the individual Colds are as common among robust athletes as among individuals leading sedentary lives Experience shows that ample clothing dry warm shoes and moderate exercise are better prophylactic measures than most hardening procedures

Patients subject to frequent colds often find relief by seeking semitropical climates during the winter months

Reports on ultraviolet radiation and vitamin feedings do not indicate a prophylactic value

Treatment —The treatment of colds consists mainly in the *relief of symptoms* as they arise Patients are usually more comfortable in bed although in most instances they prefer to continue their daily occupation Rest should be made imperative if the temperature rises above 100° F or if there is evidence of such formidable diseases as diabetes nephritis rheumatic fever cardiac lesions or pulmonary infections *Isolation* is desirable as it protects others and minimizes the opportunity of acquiring secondary infections during a phase of increased susceptibility The body especially the feet should be kept warm and dry Smoke cold damp air and other irritants should be avoided Any simple diet is suitable An occasional saline cathartic is indicated even when the bowels are active

Striking relief from malaise and aching is afforded by some of the *coal tar derivatives* Phenacetin (5 grains 0.3 Gm) with soda bicarbonate (15 grains 1 Gm) every three hours is a well known combination An excellent grippe capsule contains

Codeine sulfate	grain 1/4	015
Acetylsalicylic acid	grains v	.3
Phenacetin	grains ij	12
Caffeine citrate	grain ss	03

If discomfort is marked one of these may be given as often as every three hours

Measures to promote sweating and vasodilatation also add to the comfort of the patient Hot foot baths and warm drinks are *often used to supplement analgesics such as* Dover s powders (10 grains 0 6 Gm) or whisky

Medication should be instituted as early as possible to diminish the hyperemia of the mucous membranes Spraying with 1.5 per cent ephedrine hydrochloride in normal saline every three hours is recommended if the drug is well tolerated Inhalation of Benzedrine from a patented inhaler is more convenient for the ambulatory patient These drugs not only relieve the stuffiness in the nostrils and help maintain adequate drainage from the nose but perhaps shorten the attack by diminishing the initial injury to the mucous membranes that follows intense congestion

Patients with laryngitis or tracheitis

should rest the voice Violent coughing should be controlled by codeine in sufficient doses if the usual emulcent or expectorant cough mixtures prove ineffectual Relief is also afforded by inhalations from a vessel containing about a pint of hot water and a teaspoonful of compound tincture of benzoin or oil of pine

Tender glands in the neck are best treated by intermittent application of ice bags

Pain and tightness under the sternum is benefited by counterirritants such as turpentine liniment mustard plasters, or flaxseed poultices

The possibility of acute pyogenic complications such as sinusitis or otitis media must constantly be considered Many of these subside spontaneously with conservative treatment therefore operation in most cases should be deferred until the need for surgical drainage is imperative

The oral administration of the sulfonamides which is not indicated in the treatment of acute colds may be beneficial when secondary bacterial infections develop Reports are favorable on the local use of these drugs such as 5 per cent suspensions of microcrystalline sulfathiazole in acute colds as prophylaxis against pyogenic complications but further confirmation is needed

Rest with a vacation is important after a severe cold It is unwise to permit patients to return to full activity in a weakened condition Nourishing food sunlight and avoidance of fatigue are essential Tonics especially those containing nux vomica or cod liver oil are beneficial

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INFLUENZA

Definition—Influenza is a highly contagious specific infectious disease which occurs most characteristically in epidemic and pandemic outbreaks during which it spreads with extraordinary rapidity The principal manifestations are sudden onset with fever marked prostration severe aching pains in the back and extremities conjunctival injection and a rapidly progressive inflammation of the respiratory mucous membrane It is self limited and of short duration Rarely serious in its uncomplicated form it often becomes so because it predisposes to frequent and highly fatal secondary infections of the lungs

History.—Although there is little doubt that influenza is a disease of great antiquity its authentic history according to Leichtenstern begins with the European epidemic of 1510 Since that time numerous epidemics have been recognized and recorded in all parts of the world At least eight great pandemics with their preceding and succeeding epidemics have occurred—1580 1729–30 1780–82 1830–33 1836–37 1847–48 1889–92 and 1918–20

Epidemiology—The history of influenza shows that great pandemics sweep the world at irregular intervals and that less severe more circumscribed epidemics occur fairly frequently during interpandemic periods

Pandemic influenza typically exhibits *three major waves* separated from each

other by a distinct interval of several months The *first wave*, though it affects great numbers of persons is relatively mild and is not attended by a high incidence of complications Its duration in a single community may vary somewhat in different localities but is always short—three to six weeks The *second wave* also attacks great numbers of persons but is more severe than the first and is accompanied by a high incidence of complications especially pneumonia with a resultant excessive mortality Like the first wave its onset is explosive in nature, reaching its peak in two to three weeks but the period of decline may be somewhat less rapid and is not infrequently interrupted by a period of recrudescence The *third wave* develops more slowly, the peak is not sharp and the period of decline is less rapid While the number of persons attacked is somewhat less complications are frequent and severe This alteration in the characteristics of the successive waves of pandemic influenza may be due in part to a partial immunity of those previously attacked in part to variations in the prevalence and kind of secondary infections which so frequently complicate the disease

The *morbidity* from influenza during pandemic outbreaks is very high, the best statistical studies placing it between 200 and 400 per 1000 While people of all ages are susceptible the *highest* incidence is between the ages of five and forty

Influenza which occurs in more or less localized outbreaks during interpandemic periods is now distinguished from pandemic influenza by designating it *epidemic influenza* It has occurred in many parts of the world at irregular intervals of one to four years since the last pandemic ended in 1919 It differs from pandemic influenza in being less severe and in having a lower attack rate usually between 10 and 20 per cent

The exact relationship between epidemic and pandemic influenza is still uncertain Lack of complete knowledge concerning the immunologic relationships of different strains of influenza virus and lack of opportunity to investigate the etiology of pandemic influenza by the methods which have proved successful in epidemic influenza make it impossible to answer this problem at the present time

In addition to the recurrent cyclic nature of both pandemic and epidemic influenza the most characteristic epidemiologic features are the explosive nature of the outbreaks the rapidity of spread the high attack rate and the relatively short duration of the individual waves All of these features may be explained by the combination of a fairly general susceptibility a short incubation period and the brief self limited course of the uncomplicated disease Other contributing factors may be found in the fact that many who are attacked continue to work and thus spread the disease and in the ready transmissibility of primary respiratory infections The rapidity of spread is further influenced in any given area by the rapidity of the existing means of travel and the extent of human intercourse being more rapid in thickly settled communities less so in sparsely populated districts Presumably dissemination occurs directly from person to person through contact and droplet infection by talking coughing or sneezing

Etiology —The epidemiologic and clinical features of pandemic and epidemic influenza suggest that it is caused by an easily transmissible infectious agent possessing a high degree of primary pathogenicity for man The theory that *Hemophilus influenzae* is the specific cause of influenza which was generally accepted until the pandemic of 1918 has since been abandoned in favor of the view that the primary incitant is a filtrable virus Convincing evidence in support of this latter view in so far as epidemic influenza is concerned was provided in 1933 by Smith Andrewes and Laidlaw who succeeded in isolating a filtrable virus from patients with influenza by inoculating ferrets intranasally with filtrates of throat washings from early cases The infection was transmitted from ferret to ferret and subsequently to mice These observations have been amply confirmed by Francis Burnet, Smorodintseff and others from many parts of the world Though it was believed at first that all strains of virus from various parts of the world were serologically identical it would now appear that not only different epidemics but even the same epidemic may be caused by immunologically distinct races of influenza virus At least two which are

designated influenza A virus and influenza B virus respectively, have been identified and doubtless others exist While the foregoing studies have dealt only with epidemic influenza it seems probable that they will be found applicable to pandemic influenza Whether or not pandemic influenza will be found to be due to a strain of virus different from those so far isolated or to be a symbiotic infection comparable to swine influenza (Shope), only future study can determine

Bacteriology —Many bacteria play a significant role as secondary invaders especially in pandemic influenza The most frequent is *Hemophilus influenzae* which is commonly found in large numbers in the secretion of the respiratory tract during life At necropsy it is frequently encountered in the pus from infected sinuses and in the exudate throughout the bronchi and bronchioles It is less often found in the parenchyma of the lung and only rarely invades the pleura pericardium or blood Other important secondary invaders are *Pneumococcus Streptococcus haemolyticus* and *Staphylococcus aureus* Organisms less frequently met with are *Streptococcus viridans Staphylococcus albus Micrococcus catarrhalis Friedlander's bacillus* and *Meningococcus*

Morbid Anatomy —So far as is known simple uncomplicated influenza causes no characteristic changes which serve to differentiate it from other catarrhal inflammations of the respiratory mucous membrane In severe rapidly fatal cases of influenza with pneumonia there is in addition to the rhinitis and pharyngitis an intense tracheitis and bronchitis often hemorrhagic a very marked bronchiolitis with epithelial necrosis and serosanguineous exudate in the lumen peribronchiolar and hemorrhagic pneumonia marked alveolar edema and emphysema with a characteristic hyaline fibrin lining the distended air spaces and little or no pleural involvement In cases in which secondary infection dominates the picture the pulmonary pathology is complex Noteworthy characteristics referable to infection with *Hemophilus influenzae* are bronchitis purulent bronchiolitis often leading to bronchiectasis and peribronchiolar and atrial pneumonia while those referable to the pyogenic cocci are interstitial and confluent lobular pneumonia often attended by necrosis abscess formation and a marked tendency to organizing pneumonitis Mediastinitis and empyema frequently occur when hemolytic streptococci are present (Opie, *et al* Winternitz, *et al*)

The *paranasal sinuses* often show intense *inflammation* of their mucous membranes and contain purulent exudate Hemorrhages may occur in the skeletal muscles especially in the *rectus abdominis* also in the pericardium spleen kidneys adrenals testes and cerebrum *Interstitial emphysema* of the pleura lungs mediastinum and neck is sometimes found Other lesions which may be found at autopsy are referred to below under Complications

Symptoms —The *incubation period* lasts from one to three days usually about forty to forty eight hours The *onset* is sudden with fever chilly sensations and prostration usually accompanied by catarrhal symptoms referable to the nose the pharynx or the trachea Depending upon the severity of the infection the subsequent course of the disease is so variable that it can best be described by division into types

Simple Form without Complications —Simple uncomplicated influenza comprises more than 95 per cent of the cases during the first wave of a pandemic 70 to 90 per cent in the subsequent waves and is the form commonly encountered in epidemic influenza The *onset* is usually sudden without a period of invasion The initial symptoms are chilliness extreme general malaise and severe aching pains throughout the whole body but especially in the back and extremities *A varying degree of prostration* sometimes leading to complete collapse is almost invariably present Severe headache is common Stupor or delirium occasionally occurs The temperature rises rapidly ranging from 100° to 106° F in most cases being between 102° and 106° F The pulse rate varies between 80 and 100 and the respiration rate is slightly accelerated The patient appears listless the face and often the neck and upper thorax are deeply flushed the conjunctivae are injected the pharyngeal mucosa is intensely congested The soft palate often exhibits a punctate erythema sometimes a petechial rash Shortly after onset coryza begins or sore throat due to *the pharyngitis or soreness* behind the

manubrium sterni with a dry irritative cough due to tracheitis Whether the respiratory symptoms are an essential phenomenon of influenza or are a secondary manifestation is not entirely certain They are unquestionably present in the vast majority of patients and have been considered by most clinicians to be an integral part of the disease Epistaxis is fairly frequent occurring in 10 to 15 per cent of the cases Gastro intestinal symptoms are usually slight nausea vomiting and diarrhea being rare except in children At this age gastro intestinal disturbances frequently dominate the picture

The *subsequent course* of the disease is brief The fever persists for from one to five days in the majority of cases from two to four days It is often diphasic in character The respiratory symptoms become more marked usually being well developed at the end of twenty four hours They may remain localized in the nose the pharynx or the trachea but more commonly spread rapidly throughout the respiratory tract, sometimes as far down as the large bronchi The progress of respiratory infection is marked subjectively by sensations of irritation stinging and a feeling of tightness A thin mucoid exudate appears which later may become mucopurulent With the development of tracheitis there is a sense of burning and tightness beneath the sternum accompanied by a harassing cough The sputum which at first is scanty mucoid and sometimes streaked with blood later becomes mucopurulent Laryngitis may develop Examination of the chest reveals little abnormality except when involvement of the large bronchi gives rise to scattered rhonchi and sibilant rales

Examination of the *blood* shows a leukopenia in most cases during the acute stage although in the mildest cases the white count may be normal or even slightly elevated Although opinion differs as to the nature of the leukopenia it would appear to be predominantly a lymphopenia Blood cultures are usually sterile The *urine* frequently shows a febrile albuminuria

Recovery is prompt the temperature usually falling by rapid lysis occasionally by crisis Although convalescence is rapid in most of the simple cases it may be attended by a prolonged period of depression and asthenia In the absence of secondary complications *relapses* do not occur and there are no fatalities in this type of the disease

Simple Form with Complications—Between the simple uncomplicated form of influenza and the severe pneumonic form there is a type which is prolonged by the development of a purulent bronchitis or sinusitis or both The bronchitis begins insidiously without any prominent symptoms to mark its onset About the third or fourth day when recovery from the primary disease is expected the patient begins to cough more frequently and to raise increasing amounts of mucopurulent sputum This may be quite abundant and is often somewhat nummular in character It frequently shows the presence of *Hemophilus influenzae* together with one or more other organisms such as *Pneumococcus Streptococcus* or *Micrococcus catarrhalis* Examination of the chest reveals numerous coarse medium and fine moist rales scattered throughout the lungs usually most numerous over the lower lobes The percussion note breath and voice sounds and vocal and tactile *fremitus* remain normal A moderate elevation of temperature rarely above 101° F and of irregular character usually persists for a few days or a week There is little or no increase in the respiration or pulse rates and cyanosis is unusual in the absence of bronchopneumonia In many cases a persistent cough due to chronic bronchitis continues for weeks Sometimes a mild degree of chronic bronchiectasis results Mucopurulent sinusitis affecting any or all of the paranasal sinuses may be a distressing complication accompanied by severe headaches prolonged fever and prostration Otitis media also occurs more commonly in children

This form of the disease comprises 10 to 15 per cent of the cases in the second and third pandemic waves and is also not infrequently encountered in epidemic influenza

Pneumonic Form—During the second and third pandemic waves from 5 to 15 per cent of all patients develop pneumonia In a large majority of instances the pneumonia is caused by a mixed infection of the bronchi and lungs with *Hemophilus influenzae* and one or more associated organisms the most common being *Pneumococcus Streptococcus*

haemolyticus and *Staphylococcus aureus* Of the pneumococcus infections 85 to 90 per cent are caused by the ordinary mouth pneumococci In some cases *H influenzae* alone is found In a few instances of fulminating rapidly fatal infection no organisms have been found The pathology and to some extent the clinical course of the pneumonia is determined by the bacteria concerned (Opie *et al*) It is clear that pneumonia in general should be regarded as a complication of primary influenza even though a limited number of cases may occur in which the disease is pneumonic from the outset and fatal before secondary organisms invade the lungs

Clinically the pneumonic form may be divided into three types which it is true overlap in any large series of cases These are (1) a fulminating rapidly fatal form in which pneumonia is present from the outset (2) a progressive form in which on the second to fourth day the signs of pneumonia begin to develop without the appearance of any decline in the fever (3) a late form in which after apparent recovery from the primary influenza pneumonia suddenly supervenes on the fourth to tenth day after onset

In the first form which is comparatively rare and ordinarily occurs only during the rise and height of the second pandemic wave the onset in addition to the symptoms of simple influenza is accompanied by great respiratory distress intense cyanosis and signs of rapidly developing hemorrhagic edema of the lungs The condition is very alarming Patients thus affected may die within twenty four to forty eight hours

The second and third forms differ only in time of onset of the pneumonia and may be discussed together The primary influenza is the same as in the simple form The onset symptoms physical signs and course of the pneumonia are very variable ranging all the way from those of a mild bronchopneumonia with limited pulmonary involvement from which there is prompt recovery in four or five days with defervescence by lysis or crisis to those of a rapidly progressive coalescing pneumonia with fatal outcome In some cases the picture is that of lobar pneumonia in others there is a long drawn out course due to necrotizing or organizing processes Certain features deserve special consideration In many cases the areas of pneumonia are isolated and deep seated so that in spite of the severity of the condition the typical signs of consolidation do not appear until comparatively late The involvement is nearly always bilateral The signs usually appear first over the lower lobes and are apt to vary greatly from day to day as the disease progresses The temperature curve is very irregular The pulse except during the last thirty six hours in fatal cases is apt to be slow in proportion to the temperature The respiratory rate varies with the severity of the disease Cyanosis which is a prominent feature is largely of the lilac or heliotrope type and indicates insufficient oxygenation of the blood as it passes through the lungs Early pleurisy except in hemolytic streptococcus infections and in the rapidly coalescent cases is uncommon The character of the sputum varies It may be scanty bloody and mucoid or profuse purulent salmon pink or yellowish green the latter type being associated with an extensive bronchiolitis or bronchiectasis The leukopenia of the primary influenza frequently continues throughout the course of the pneumonia especially in the severe cases A relative polycythemia often occurs when the disease is rapid and severe the red blood cell count sometimes reaching 8 000 000 per cubic millimeter Blood cultures are rarely positive except as a terminal event the serious features of the disease probably being due to toxemia and anoxemia rather than to septicemia Recovery is frequently delayed by the formation of abscesses and by failure of resolution Sudden death occasionally takes place during apparent recovery Convalescence is often prolonged Chronic bronchitis and bronchiectasis are frequent sequelae

Complications —Influenza predisposes to secondary infection with a variety of organisms Whether this is preponderantly due to lowering of general resistance by the extreme prostration of the disease and the inhibition of leukocytic defense or to a destruction of local resistance against bacterial invasion by profound injury to the respiratory mucosa or to a combination of

both factors is uncertain It seems most probable that both are concerned At any rate, complications are numerous and varied and in large part determine the mortality of the second and third pandemic waves The most frequent and important complications are acute sinusitis otitis media with or without acute suppurative mastoiditis purulent bronchitis and bronchiolitis bronchiectasis and pneumonia The pneumonia itself may be complicated by the development of pulmonary abscesses especially when *Streptococcus haemolyticus* or *Staphylococcus aureus* are present. Empyema is common in the streptococcus cases and usually begins relatively early in the course of the pneumonia Mediastinitis pneumothorax and interstitial emphysema may occur

Erythema, simple purpura and subcutaneous abscesses occasionally appear Herpes is infrequent Rupture of the rectus abdominis muscles with hematoma has been noted in a considerable number of cases Epistaxis is frequent hemoptysis and hemorrhage from the bowel much less so The circulatory system is not commonly affected but pericarditis endocarditis and thrombophlebitis are occasional complications A postinfluenzal bradycardia sometimes develops Tympanites is frequent in the toxic pneumonic cases and a moderate icterus may develop Peritonitis is a rare complication Arthritis and osteomyelitis have been observed with influenza Nephritis is rare Meningitis hemorrhagic encephalitis and multiple neuritis occasionally occur Transient postinfluenzal psychoses are seen

The *commonest sequelae* are chronic bronchitis chronic bronchiectasis and pulmonary fibrosis These conditions may persist throughout life and not infrequently lead to a mistaken diagnosis of pulmonary tuberculosis

Diagnosis —There is no single pathognomonic feature upon which a diagnosis of influenza may be made During pandemics however the diagnosis is not difficult in the majority of cases The sudden onset of a febrile attack with severe prostration and aching pains in the back and legs which are out of proportion to the catarrhal symptoms together with the flushed face injected conjunctivae intensely congested pharynx and a leukopenia are the characteristic manifestations When there are numerous other cases the foregoing features warrant a diagnosis of influenza During interpandemic periods the diagnosis is even more difficult unless substantiated by isolation of the virus or by appropriate immunologic tests which demonstrate an increase in specific antibody titer during convalescence The recognition of complications depends upon the characteristic symptoms and physical signs of the condition in question Whenever the fever persists for more than four days a complication should be suspected and carefully looked for

Prognosis.—The prognosis of simple uncomplicated influenza is excellent In cases with the less serious complications such as sinusitis laryngitis and bronchitis the prognosis is also good and recovery takes place unless further complications develop Purulent bronchiolitis and bronchiectasis however may result in chronic pulmonary disease which persists for years with periods of exacerbation and remission With the onset of pneumonia the prognosis becomes serious the mortality rate varying all the way from 15 to 60 per cent under varying circumstances The degree of cyanosis and the rate of respiration are probably the two most important prognostic signs A persistent progressively increasing cyanosis particularly of the heliotrope type and a progressively increasing tachypnea nearly always indicate a fatal outcome Even when patients appear to be doing well a sudden change for the worse may supervene at any time so that prognosis should be cautious until convalescence is well established In pregnancy the prognosis is always serious the mortality high

Prophylaxis —While there is at present no specific prophylaxis of proved value for preventing influenza in man, it has been shown that ferrets and mice can be successfully immunized against the experimental disease and that protective antibodies develop in the blood serum of human subjects following subcutaneous injection of influenza virus vaccine There is also some evidence that a high titer of specific humoral antibodies is one expression of relative immunity to the natural disease and that vaccination with influenza virus vaccine enhances resistance Further study of this problem is

necessary however, before vaccination can be recommended

Complete isolation is a preventive measure of proved though little practical value except under very exceptional circumstances Individuals should avoid contact with known cases during epidemic outbreaks

Treatment —There is no specific cure for influenza The most important forms of treatment are (1) absolute confinement to bed *from the onset of the disease until convalescence is well established* and the danger of complications is past (2) administration of large quantities of fluid (3500 to 5000 cc daily) during the febrile period (3) isolation from sources of secondary infection and the practice of medical asepsis by those coming in contact with the patient If these are rigidly adhered to the incidence of complications may be greatly reduced During the acute period the diet should be light For the headache an ice cap should be employed and if necessary aspirin 0.3 to 1 Gm (5 to 15 gr) may be given It is also of value for relief of the general aches and pains If there is sleeplessness Dover s powder 0 6 Gm (10 gr) may be used A simple enema should be given to relieve constipation The use of an inhaling mask is of value in allaying the irritation of the respiratory mucous membranes Five to 10 drops of the following mixture should be placed on the sponge at intervals as necessary menthol 1 part, creosote 1 part chloroform 1 part

The treatment of the complications does not differ from the treatment of pneumonia sinusitis etc in general and is presented in the appropriate chapters

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DENGUE

Definition —Dengue or breakbone fever' is an acute specific febrile disease caused by a filtrable virus and transmitted by mosquitoes of the genus *Aedes* It is characterized by sudden onset with fever and prostration and by intermission of fever on the third or fourth day with recurrence after eighteen to thirty hours A rash appears during the period of apyrexia or with the second rise in temperature The duration is seldom longer than seven days

History.—The first known epidemics of dengue occurred in Egypt and Java in 1779 a year later Philadelphia experienced the severe outbreak described by Rush It is possible that a disease recorded in Seville during the seventeenth century was dengue During the past one hundred and fifty years many widespread epidemics have occurred in the southern United States and in many other areas

Incidence —Dengue occurs wherever the mosquito *Aedes aegypti* abounds and climatic conditions are suitable for the survival of the virus in this vector It is endemic in the tropics and mildly so in certain subtropical and even temperate regions During the past twenty years there have been severe epidemics in the Southeastern and Gulf states of the U S in Australia Egypt and in Greece Between epidemics sporadic cases are occasionally seen

Mode of Transmission —In 1903 Graham suggested that dengue was transmitted by mosquitoes and suspected *Culex fatigans* Four years later Ashburn and Craig working in the Philippines demonstrated that the causative agent could be transmitted by blood that it was filtrable and that a mosquito was the vector though they erroneously implicated *Culex quinquefasciatus* In 1916 Cleland Bradley and McDonald in Australia showed that *Aedes aegypti* could transmit the disease but that Culicine mosquitoes could not be infected This observation was confirmed by Koizumi and his collaborators and by American investigators in

the Philippines The latter group demonstrated that *Aedes albopictus* could also be infected A mosquito having once ingested the blood of a person with dengue is able to transmit the disease during the remainder of its life though Blanc and Caminopetros found that the virus became noninfective when mosquitoes known to carry it were kept at temperatures below 20° C (64 4° F) This observation probably explains the rapid subsidence of epidemics of dengue with the advent of cool weather

Period of Infectivity —While Blanc and Caminopetros were able to transmit dengue with intravenous injections of patients blood taken during the first five days of illness Simmons St John and Reynolds showed that for mosquitoes to become infected it was necessary for them to ingest blood during the first forty eight hours They also proved that there is then a period of extrinsic incubation or presumable multiplication of the virus in the mosquito of at least nine days usually twelve before the vector is able to infect by its bite

Immunity —An attack of dengue produces transient immunity probably for not longer than five years in most individuals perhaps as long as ten in some Major epidemics in certain localities have occurred at five-year intervals affecting from 50 to 60 per cent of the population on each occasion No protection is afforded by the injection of convalescent serum or blood nor is filtered infectious plasma or serum rendered avirulent by treatment with immune serum Second and third attacks are apt to be mild and somewhat atypical

Etiology —The specific causative factor of dengue is a filtrable virus capable of passing Chamberland candles L_2 and L_3 It resists refrigeration for at least fifty four days and drying for at least ten months Koizumi was able to transmit the disease by injection of as little as 0 00005 cc of blood drawn during the first febrile period Experimental animals do not show fever or symptoms after inoculation but Blanc and Caminopetros observed that the blood of guinea pigs was infectious for human subjects five days after the injection of virulent blood or serum They also produced a transient asymptomatic and afebrile carrier state in some nonimmune human subjects

Epidemiology —Noteworthy epidemics of dengue occur when there is a coincidence of free propagation of *Aedes aegypti* with waning immunity of the human population Such conditions exist when after a period of five or more years there are unusual warmth and abundant rainfall during the late summer and early autumn in almost any locality between the parallels 32° 50 North and 23° 25′ South *Aedes aegypti* is thoroughly domesticated and able to breed in very small amounts of water so that the innumerable containers present in any center of population offer optimum facilities for oviposition Since dengue is mildly endemic throughout its distribution and it has been shown that some infected individuals remain free from symptoms an excessive number of mosquitoes soon become infected An epidemic of dengue spreads with rapidity comparable only to pandemic influenza In Athens 80 to 90 per cent of the population were ill during the epidemic of 1928–29 and in the 1934 epidemic in Florida at least 30 per cent of the permanent residents of Miami were infected While some epidemics depend on the local introduction of infected persons or mosquitoes it is likely that the unrecognized endemic disease is of paramount significance The epidemiology of dengue is important since it reflects the potential distribution of yellow fever *Aedes aegypti* being the vector of the virus of both diseases

Morbid Anatomy —Few valid observations on the pathology of dengue are available since death in uncomplicated cases is very rare Bensis saw five autopsies during the 1928–29 epidemic in Greece The gastrointestinal tract showed petechial hemorrhages probably related to the exanthem There were nonspecific parenchymatous changes in the myocardium skeletal muscles and liver The kidneys showed glomerulitis and interstitial infiltration with leukocytes The meninges were congested and the brain showed proliferation of glial cells and some leukocytic infiltration The lymph nodes were moderately enlarged as was the spleen

Symptoms and Signs —The incubation period has been shown to be from four to ten days Onset is abrupt with severe headache often localized behind the eyes pain on moving the eyeballs lumbar backache and extreme prostration Occasionally there is rigor

and children may have convulsions Loss of the sense of taste and complete anorexia are usual nausea and vomiting frequent and constipation almost constant The temperature rises in a few hours to 102° to 104° F and may reach 106° F Relative bradycardia is the rule and some patients have heart rates as low as forty Systolic blood pressure is depressed often below 100 mm of mercury and the pulse may be dicrotic During the first few hours all the larger joints particularly those of the knees hips and vertebrae become intensely painful so days, there is then rapid defervescence accompanied by profuse sweating and often diuresis sometimes there is epistaxis or diarrhea All symptoms are greatly improved during the period of intermission which is most often of twenty four hours duration There is then a second rapid rise in temperature to 102° to 103° F all symptoms recur and the characteristic rash appears This is almost always scarlatiniform but varies in distribution Typically it appears first over the knees ankles and elbows which may show periarticular swelling The entire

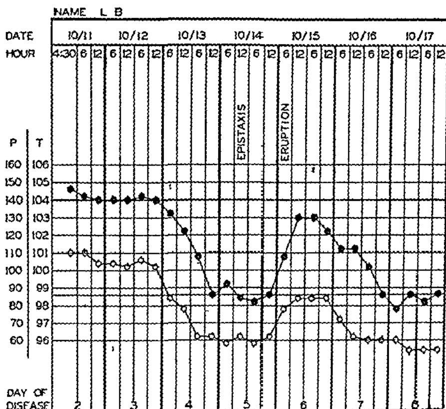


Fig 1 —Temperature chart of a patient with dengue

that motion is almost impossible though passive movement may be tolerated A transient pale pink macular rash is often seen at the onset The face is flushed the conjunctivae and sclerae are much congested and mild injection of the pharynx is common Some glandular enlargement is present in about three fourths of the cases the epitrochlear inguinal and posterior cervical nodes being most frequently palpable The spleen is not infrequently felt just below the costal border and is quite soft Fever and symptoms persist for three sometimes four body except the face may be involved or there may be a patchy distribution over the trunk and the flexor surfaces of the extremities The palms and soles are bright red and often so edematous that flexion of the hands and feet is painful Some patients have marked pruritus before or with the eruption The rash and symptoms persist until final defervescence which occurs with great regularity after two days on the sixth or seventh day of illness Desquamation is frequent Certain cases are atypical in that the second febrile period does not occur Convalescence

is apt to be slow, bradycardia hypotension and asthenia may persist for weeks

The blood constantly shows leukopenia due to granulocytopenia The leukocyte count is usually between 2000 and 6000 with 20 to 45 per cent of granulocytes Many of the polymorphonuclear cells show toxic or degenerative changes vacuolization, pyknosis and fragmentation of nuclei basophilic granulation and vacuoles in the cytoplasm are common Coles has described minute round and oval diplococcoid bodies in the red cells which are demonstrable by prolonged staining with dilute Giemsa Their significance is not established

The urine is often scanty and concentrated from vomiting and inadequate intake of fluids Albuminuria and cylindruria are seldom more than fever would explain

Complications—Bleeding from the nose gastro intestinal tract and uterus may occur and seem to have been unusually common in the Greek epidemic Heart failure and acute renal insufficiency have been observed in patients with arteriosclerosis The syndrome of neurocirculatory asthenia is a rather frequent sequel to dengue

Diagnosis—Illness beginning suddenly with headache muscle and joint pains nausea and fever during a time when *Aedes* mosquitoes are abundant should suggest dengue At the onset it may be mistaken for influenza malaria or measles In areas where typhus or yellow fever are endemic it may be confused with them Seen first after the exanthem has appeared it may suggest scarlet fever In unvaccinated individuals smallpox may be suspected The course of the illness speedily differentiates influenza and measles malaria can be excluded by examination of the blood Leukopenia and bradycardia rule out typhus even before the characteristic remission of fever and eruption Yellow fever can be eliminated by absence of icterus and albuminuria Lack of angina of marked cervical adenitis and of leukocytosis serves to differentiate dengue from scarlet fever but occasionally smallpox cannot be excluded until the eruption appears

Prognosis—Death from uncomplicated dengue probably occurs in less than 1 case in 10 000 In severe epidemics the rate may far exceed this because of prevalence of the disease among the higher age groups with advanced vascular disease of the brain, heart or kidneys

Prophylaxis—Personal prophylaxis includes avoiding *Aedes* mosquitoes and the use of mosquito nets and repellants All patients should be kept under close mosquito nets and all measures taken to destroy mosquitoes and their breeding places on the premises Communities should make every effort to eliminate actual and potential breeding places Blanc and Caminopetros were able to produce apparent immunity by vaccination with infectious serum treated with bile

Treatment—This is entirely symptomatic Pain is often mitigated by codeine 0 033 Gm (grain 1/2) and acetylsalicylic acid 0.333 Gm (grain v) given as frequently as necessary codeine 0 066 Gm (grain i) or morphine 0 008 Gm (grain 1/8) given hypodermically may be required when nausea is severe atropine should be combined with these Ice caps to the head cold sponges or packs and cool rectal irrigations give some relief from fever For nausea chloretone 0.2 Gm (grain iii) repeated each hour for three or four doses is often effective though the favorite remedy is calomel 0 006 Gm (grain 1/10) every half hour until the bowels move Diet should be liquid and fluids forced to tolerance Fluids must be given parenterally when nausea prevents an adequate intake by mouth During convalescence the diet should be increased slowly Rest is essential and should be prolonged in the cases of elderly individuals

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YELLOW FEVER

Definition —Yellow fever is an acute disease caused by a filtrable virus and characterized in severe and typical cases by sudden onset prostration, moderately high fever a pulse rate slow in relation to temperature vomiting of altered blood albuminuria and jaundice It occurs in certain tropical and subtropical countries but epidemics have extended far into the Temperate Zone during warm seasons There is but one yellow fever by clinical or immunologic criteria but the disease is classified on an epidemiologic basis as aegypti transmitted when the virus is transferred by the mosquito *Aedes aegypti* the long recognized vector under urban and some rural conditions or as jungle yellow fever when it occurs in a forest or jungle environment in the absence of that mosquito The aegypti transmitted disease involves man primarily and is perpetuated in the recurring cycle man aegypti man but jungle yellow fever is presumably an infection of unidentified animals which is occasionally transferred to man particularly to young adult males who work in the forest by jungle mosquitoes or other arthropods not yet fully identified

Etiology —The cause of yellow fever is one of the smaller filtrable viruses By filtration through gradocol membranes its diameter has been found to lie between 17 and 25 millimicrons It can be preserved for at least ten years by thoroughly drying virus containing serum in the frozen state sealing in glass and storing at low temperatures

The virulence of yellow fever virus on account of differences in tissue affinity is of two kinds which may vary independently Viscerotropism in yellow fever virus gives the power to attack principally the liver kidneys and heart while neurotropism results in damage to the nervous system When both properties are present the virus is pantropic and it is in this form that it is found in nature No purely viscerotropic strain of yellow fever virus has been produced in the laboratory but strains acquire a heightened neurotropism and almost entirely lose their viscerotropism during long passage through mice by intracerebral inoculation Both virulences have been greatly reduced by prolonged cultivation in certain types of tissue culture

Man is highly susceptible to the natural pantropic virus and the characteristic lesions of yellow fever in man are due to its viscerotropism Whether the nervous system of man is ever directly involved in natural infections is subject to doubt Some brain symptoms which have been reported may have been due to hemorrhage or a toxic factor The rhesus monkey (*Macaca mulatta*) is even more susceptible than man to pantropic virus and it reacts in a similar way If a rhesus monkey is inoculated intracerebrally with a highly neurotropic strain a severe and usually fatal encephalitis results and there are ordinarily no evidences of viscerotropism Other monkeys are susceptible in varying degrees and many are practically insusceptible Mice especially certain selected laboratory strains are highly susceptible to the neurotropic virulence but insusceptible to the viscerotropic The white rat is insusceptible to both virulences The European hedgehog (*Erinaceus europaeus*) is highly susceptible to both Some other animals show few symptoms but are sufficiently susceptible to permit the multiplication of virus and practically all animals tested are capable of producing protective antibodies if given large inoculations of living virus

In aegypti transmitted yellow fever the mosquito *Aedes aegypti* formerly called the stegomyia transmits the disease by biting a person during the first three or four days of yellow fever the period in which the virus circulates freely in the blood and later biting a susceptible person An interval of from nine to twelve days or more depending largely on temperature must elapse before the mosquito will become infectious through biting but throughout this incubation period the virus in the insect is infective if its body is ground up and injected Much shorter and longer incubation periods in the mosquito have been observed under extremes of temperature in laboratory experiments There is definite multiplication of the virus in the mosquito at favorable temperatures

In jungle yellow fever the virus most probably is transmitted by mosquitoes or other arthropods Under laboratory conditions 17 mosquitoes from various parts of the world in addition to *Aedes aegypti* are capable of transmitting yellow fever by biting These are in Africa *Aedes luteocephalus Aedes stokesi Aedes vittatus Aedes africanus Aedes simpsoni Aedes taylori Aedes metallicus Eretmopodites chrysogaster Mansonia africana* and *Culex thalassius* in South America *Aedes scapularis Aedes fluviatilis Aedes leucocelaenus* and *Haemagogus capricorni* in the East Indies *Aedes albopictus* in Europe *Aedes geniculatus* and in North America *Aedes triseriatus* Specimens of two of these *Aedes leucocelaenus* and *Haemagogus capricorni* wild caught in areas of South America were found to contain yellow fever virus and to be able to infect monkeys by biting Likewise in Africa *Aedes simpsoni* wild caught in the Bwamba forest of Uganda were recently found to contain yellow fever virus It remains to be shown which of the numerous biting insects of the forest play the dominant role in the transmission of yellow fever

Numerous accidental laboratory infections in the absence of aegypti have suggested that man may be infected through contact of the virus with unbroken skin or mucous membranes Experiments with monkeys have shown that pantropic yellow fever virus in blood may pass through unbroken skin and cause the disease Monkeys and mice have been infected by intranasal instillations of neurotropic virus and mice by putting neurotropic virus into the conjunctival sac

Infection with virus of yellow fever is present only in certain parts of the world and is completely absent from many tropical and subtropical countries in which aegypti mosquitoes abound In recent years a world survey of immunity in man against yellow fever was carried out by testing many thousands of blood specimens in mice for their power to protect against yellow fever virus In this way it was shown that immunizing infections with yellow fever virus had been recently occurring in South America and Africa in vast interior areas previously supposed not to be infected The systematic collection and examination of liver specimens in cases of febrile diseases in South America obtained from the cadaver by means of the viscerotome showed that fatal cases of yellow fever were occurring in the region in which immunity had been found Moreover epidemics of jungle yellow fever have recently occurred in the regions of observed

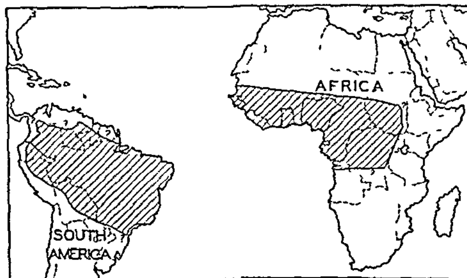


Fig 2—Approximate world distribution of yellow fever immunity (shaded areas) determined by blood tests and based on immunity acquired since 1925 in the Western Hemisphere and within the present generation in the Eastern Within the areas are the two great *endemic regions* all recognized epidemics since 1925 and coastal areas of Brazil freed of yellow fever infection by mosquito control

immunity It is believed that the two vast areas of immunity in South America and Africa contain the endemic regions from which yellow fever escapes from time to time to start urban aegypti transmitted epidemics and to spread through commercial paths Since 1938 no important outbreaks of aegypti transmitted yellow fever have been reported from the Western Hemisphere but epidemics of jungle yellow fever have been observed Epidemics of aegypti transmitted yellow fever occur frequently in West Africa and it is probable that the immunizing infection in Central Africa is similar in its epidemiology to the jungle yellow fever of South America

The knowledge of the etiologic factor in yellow fever has been acquired in several steps In 1881 Carlos Finlay of Cuba announced his unshakable belief that the disease was transmitted by the mosquito now known as *Aedes aegypti* In 1900 and 1901 Reed Carroll Agramonte and Lazear of the United States Army Yellow Fever Commission performed experiments with human volunteers in Cuba and proved that the causative agent was transmitted from man to man by this mosquito and that it could pass through a Berkefeld filter capable of holding back *Staphylococcus aureus* In 1927 Stokes Bauer and Hudson working in West Africa under the auspices of the International Health Division of The Rockefeller Foundation, showed that the common rhesus monkey was susceptible to yellow fever and used it in studying the properties of the virus In 1930 Theiler found out in Boston that the mouse also was susceptible if inoculated intracerebrally In 1931 in New York Sawyer Kitchen and Lloyd commenced vaccinating persons effectively with simultaneous subcutaneous injections of human immune serum and living neurotropic yellow fever virus In 1932 Soper Penna Cardoso Serafim Frobisher and Pinheiro described in Brazil the first epidemic in which it was proved that *Aedes aegypti* was not the transmitting agent thus revealing the existence of jungle yellow fever From 1933 to 1937 in New York Lloyd Theiler and Ricci and Theiler and Smith performed the experiments with yellow fever virus in tissue culture which resulted in the production of a profoundly altered strain 17D low in viscerotropic and neurotropic virulence and suitable for widespread vaccination

Morbid Anatomy—The skin usually has a distinct yellow color, more intense than during life and there may be petechiae or ecchymoses The mouth or nostrils are often stained with vomitus containing altered blood The liver is of normal size or slightly enlarged Its color is brownish yellow which turns usually to chamois color when the blood is drained out The stomach commonly contains varying amounts of brownish black altered blood Such blood may be found in the intestines also Petechiae are often observed in the mucosa of stomach and duodenum The spleen shows little alteration in size or general appearance The kidneys are swollen and pale, and on section the cortex is pale and yellowish The heart is pale and flabby The brain shows little surface change

Under the microscope the most characteristic and striking lesions are those in the parenchymatous cells of the liver There is profound noninflammatory necrosis and fatty degeneration This is most evident in the midzone of the lobule and a band of normal cells is ordinarily seen around the central and portal veins Scattered irregularly among the affected cells are certain ones showing acidophilic coagulative hyaline necrosis (Councilman bodies) Although acidophilic intranuclear inclusions are frequently found in the hepatic cells of experimentally infected monkeys they are rare in those of man The spleen shows degenerative changes which are most prominent in the malpighian corpuscles The kidneys show cloudy swelling necrosis and fatty degeneration of the tubular epithelial cells There is also fatty degeneration of the heart The microscopic lesion found most frequently in the brain is perivascular hemorrhage There is usually no evidence of encephalitis due to the neurotropism of yellow fever virus

Symptoms—The incubation period is commonly between three and six days but may be as long as ten Prodromal symptoms are usually absent and the onset is sudden sometimes with a chill but usually not The outstanding symptoms in the first stage of the disease which lasts two or three days are fever severe headache and backache a varying amount of pain in the legs and

prostration The face is flushed and turgid The eyes are injected and there is photophobia The tongue is pointed and bright red at tips and edges but the dorsum is grayish white Jaundice is usually absent or indistinct in the first stage The temperature and pulse rise abruptly at onset the former ordinarily to between 102° and 104° F., but sometimes higher The pulse rate usually reaches ninety or hundred beats per minute and then falls for a few days more rapidly than would be in proportion to the irregular downward trend of the temperature (Faget's sign) The pulse is full and strong at this stage Epigastric distress and tenderness nausea and vomiting of fluid without blood are common Constipation is the rule The leukocyte count is normal or low at the onset and it falls throughout this stage Albuminuria usually begins on the second day and is definite on the third

The *second stage* begins on the third or fourth day At about this time there may appear the characteristic *remission of temperature* followed by a secondary rise but this remission is often indefinite or absent It may be accompanied by a deceptive temporary improvement In this stage the face becomes pale sometimes with cyanotic tinge The headache and backache cease or diminish Restlessness gives way to lassitude and depression sometimes with mental confusion Jaundice gradually becomes visible There may be petechiae in the skin The gums are often swollen and bleed easily either spontaneously or when pressed from outside through the lip The nose may bleed The dorsum of the tongue becomes increasingly dry and brown The pulse rate falls progressively and may go below fifty This bradycardia is attributed to damage to the sino auricular node Even in otherwise mild attacks there may be marked dilatation of the heart and low blood pressure as evidence of myocardial derangement Vomiting may be frequent and distressing and the vomitus in this stage contains altered blood which settles from the clear fluid as small dark brown flakes (flywings) or masses resembling coffee grounds The leukocyte count reaches its lowest point around 3000 per cubic millimeter on the fifth or sixth day of the attack and then rises rapidly reaching normal early in the convalescence The amount of albumin in the urine rises sometimes to 5 or 6 Gm per liter The urine is acid and highly colored and contains numerous granular casts Late in the disease it may contain bile Fatal cases often exhibit hiccough copious vomiting of altered blood black stools and anuria followed by convulsions or coma Death occurs most commonly from the sixth to the ninth day but rarely a few days later If there is recovery, the temperature is likely to reach normal by the seventh or eighth day Convalescence begins then and progresses rapidly to complete recovery, with disappearance of the albuminuria True relapses probably do not occur Complications are rare A lifelong immunity follows the attack

The majority of all yellow fever cases are mild and show few of the classic symptoms described Frequently the only evident symptoms are a brief and slight fever with headache A peculiarity of yellow fever is the great variation in the degree to which the various organs are attacked With much kidney involvement there may be no heart symptoms and *vice versa* In mild and moderate cases there is frequently little or no albuminuria or jaundice

Diagnosis.—A satisfactory provisional diagnosis may be made on the basis of symptoms in many moderate and severe cases but experienced clinicians have had difficulty in distinguishing yellow fever by that criterion from leptospiral jaundice (Weil s disease) other jaundices or even malaria influenza and dengue The short course of yellow fever and the mildness of the jaundice help to distinguish it from most of the other jaundice diseases Although it takes time and requires the collaboration of a specially qualified laboratory the diagnosis may be settled by either of two standard procedures About 30 cc of blood should be drawn early in the acute disease with precautions for sterility and a similar specimen should be obtained three weeks after onset The sterile serum from each should be sent to a laboratory with facilities for making yellow fever protection tests If the first specimen fails to protect mice against yellow fever virus and the second one does the disease was yellow fever If neither protects or both protect equally the illness was some other disease In taking blood for any purpose during

the acute disease rubber gloves should be worn as the blood of yellow fever is highly infectious for the first three or four days The other method is to draw blood from the vein within the first three days of illness and inject 0 03 cc of the serum intracerebrally into each of six susceptible mice and observe them for two weeks If any one of the mice shows symptoms suggestive of encephalitis its brain should be removed emulsified in physiologic salt solution and injected into six other mice These should be sent to the laboratory in order that the virus may be isolated and identified The former method is usually the more practical For postmortem diagnosis specimens of liver and other tissues should be placed in 10 per cent formalin and sent to the laboratory

Prognosis —The cases clinically recognized and reported in a recent urban epidemic (Rio de Janeiro 1928–1929) showed a fatality rate of 59 per cent and this may be taken as representative Case fatalities ranging from 10 to 85 per cent have been cited however Negroes ordinarily have a lower fatality than whites or Orientals If the numerous mild infections were recognized the reported case fatalities would be much lower

In individual cases the prognosis early in the disease should always be guarded as sudden changes for the worse are not uncommon If symptoms are mild recovery is probable and some severe cases will end favorably but hiccough copious black vomit melena and anuria justify a grave prognosis

Treatment —There is no specific treatment At the beginning the severe headache may require relief with an analgesic The bowels should be cleared with a saline laxative Thereafter enemas should be given as needed The patient should be moved as little as possible and should be kept quiet in bed The heart should be watched If the region is one in which vector mosquitoes exist the windows and doors should be screened and a bed net used The quarters in which infection may have occurred should be disinsectized with an efficient spray to destroy all infective *Aedes aegypti* Food should in general be withheld during the acute disease but citrus fruit juices and alkaline waters such as Vichy or ordinary tap water with added bicarbonate of soda should be given freely in small draughts If vomiting interferes with giving fluids by mouth dextrose in buffered solution may be administered intravenously physiologic salt solution by hypodermoclysis and tap water by rectum If glucose is given 50 Gm in 1000 cc of physiologic salt solution may be administered intravenously three times daily accompanied by thiamine hydrochloride 2 mg ascorbic acid 50 mg and nicotinic acid amide 15 mg These vitamins may be given in the glucose solution or separately by mouth or parenterally To relieve vomiting cracked ice and cocaine hydrochloride 0 016 Gm (¼ grain) may be given by mouth and codeine sulfate 0 032 Gm (½ grain) by hypodermic injection For the fever an ice cap or cold compress may be applied to the head and the body may be sponged with cool water The mouth should be cleansed thoroughly and frequently When vomiting has ceased and the temperature is down feeding may be cautiously resumed beginning with rice water, crumbled egg yolk and chicken broth each with added lactose

For prevention individuals who expect to be exposed when visiting infected countries or investigating yellow fever should be vaccinated with an avirulent strain of living yellow fever virus such as 17D Cities under risk should protect themselves by thorough control of the mosquito vector *Aedes aegypti* by the systematic and efficient methods now available These include districting the community so that a trained inspector with flash light may visit each room in each house of his district and the surrounding premises every week Containers harboring larvae of *Aedes aegypti* should be eliminated mosquito proofed or treated with fuel oil so that they will have to be freed of adherent ova by scrubbing before they are refilled Such measures may be depended on to suppress an epidemic or render a community noninfectible

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MEASLES

(*Morbilli Rubeola*)

Definition—Measles is a highly communicable disease of world wide distribution which tends to recur in epidemic form at two to four year intervals Fever cough coryza conjunctivitis and a typical enanthem characterize the period of invasion With the appearance of the eruption there is an exacerbation of the systemic symptoms Defervescence and fading of the eruption occur simultaneously and are usually complete from seven to ten days after the onset of the illness

History—Measles was not clearly distinguished from the other exanthemata until the seventeenth century when Sydenham differentiated the disorder from scarlet fever The observations of Panum on the epidemic in the Faroe Islands in 1846 established the epidemiology of the disease in a manner which renders this work *a classic in its field* Characteristic signs especially the spots which appear on the buccal membranes in the prodromal and early eruptive stages of the disease had *been noted by several investigators* but their pathognomonic significance was recognized and stressed by Koplik in 1896 The transmission of measles by inoculation of the catarrhal secretions of patients to susceptible children was performed in 1758 by Home and was reintroduced in 1842 by Katona Controlled observations on inoculation of susceptible persons with blood of patients ill with the disease were reported by Hektoen in 1905 Anderson and Goldberger in 1910 reported transmission of the disease to the *monkey* No other experimental animal has been consistently found to be susceptible to the disease The value of the use of human immune bodies for the prophylaxis *or for attenuation of* the disease introduced by Cenci in 1905 was established by the observations in 1918 of Chapin and of Nicolle and Conseil

Epidemiology—Measles is of world wide distribution apparently uninfluenced in incidence by climate, race nationality or by social or economic status While sporadic cases may be observed at any time the disease has a striking epidemic recurrence, usually in late winter at intervals of two to four years varying with the size of the community Thus, in large cities epidemics occur at two year intervals while in smaller communities the disease may recur as infrequently as four or five years The *seasonal incidence* in the late winter and early spring months is one of the unexplained features of the epidemiology The disease is extremely communicable due apparently to a uniform susceptibility, to the ease of transmission and to the minute dosage of the virus required to produce infection The disease may occur at any age However the high degree of communicability usually results in its being a disease of early life In urban populations over half of the cases occur in children less than five years of age but during epidemics in areas from which the disease has long been absent elderly patients have been affected Over 95 per cent of adults in *urban populations and* only a slightly lower percentage in rural populations have had the disorder Measles in the pregnant woman is apt to be followed by miscarriage The disease has been observed in the neonatal period usually when the mother is suffering simultaneously from it Most mothers *are immune to measles* however and the infants of these mothers acquire an immunity due to passive transfer of antibodies to the fetus which serves to prevent the development of the disease in the infant up to four or five months of age Although the story is often obtained that a child has suffered from multiple *attacks of measles* it is infrequent that authentic instances of second attacks can be established Immunity following an attack of unmodified measles is usually permanent while the degree of *immunity following* the attenuated form has not been adequately determined

Etiology—The causative agent of measles is presumed to be a filtrable virus However until recent years various investigators have held the view that a streptococcus isolated from the blood or from the secretions of patients with *measles* might be the

etiologic agent Measles has been produced experimentally and by accident in man as a result of the inoculation of blood or secretions of patients with the disease Accurately controlled observations on the transfer of the disease to human volunteers by the inoculation of blood of patients suffering from the disorder were reported by Hektoen in 1905 Inoculation of the *Macaca rhesus* monkey with the blood and with secretions from the mouth and nose of patients with measles has resulted in the production of fever and an eruption in the animal Numerous experiments have been made in other animals but with no satisfactory results In recent years several investigators claim to have cultivated measles virus in the developing chick embryo and the histologic picture of the growth of the virus in the chick s allantoic membranes has been described Rake Shaffer and Stokes have reported cultivation of the virus of measles in chick embryos and thereby to have attenuated the virus so that it produces a milder disease when inoculated into humans The attenuated chick embryo culture virus after nine or more passages is also effective in producing the experimental disease in monkeys The virus so prepared is difficult to maintain requiring special arrangements for storage even at refrigerator temperatures Confirmation of these investigations especially a more extensive experience with inoculation measles and of the immunity resulting from inoculation with the attenuated virus as well as observations to determine whether the attenuated virus will revert in one or two human passages to a more virulent form must be made before inoculation with cultivated virus may be recommended

Dissemination—Measles is apparently transmitted through the secretions from the eyes and the respiratory passages with infectivity highest in the preeruptive stage Direct contact and droplet infection are the usual modes of dissemination although spread by air-borne infection through so called droplet nuclei is possible The virus is thought to be short lived outside the body and not readily transmitted by a third person the rapid spread of the disease is deemed to be due to the high degree of infectivity and the almost complete lack of resistance in individuals who have not previously experienced it Infectivity apparently subsides rapidly after the appearance of the rash and is thought to cease after the rash has begun to fade It is well established that complications of measles other than those specifically due to the virus such as the encephalitis will not spread the disease Thus a postmeasles bronchopneumonia might transmit the secondarily invading organisms but would not be a source of spread of measles The numbers of cases of measles which occur in an epidemic often are quite large so that from 80 to 95 per cent of susceptive individuals in a community will be attacked in a single epidemic Thus unlike certain other communicable diseases in which a few cases suffice to make an epidemic the number of cases of measles in an epidemic in a large community may run into thousands In 1940 276 032 cases of measles with 681 deaths were reported in the United States

Pathology.—The lesion in the skin in measles consists of a proliferative and exudative reaction in the capillaries of the deeper layers of the skin with an extension of the exudate of serum and endothelial leukocytes to the epidermis in the hair sheaths and the sebaceous glands When the rash becomes apparent the lesions have already reached their peak A desquamation in the form of fine branny scales follows measles The Koplik spots observed in the buccal mucosa correspond to the minute early lesions in the epidermis The Koplik spots tend to macerate or become somewhat eroded and lose their characteristic appearance on the second or third day of their presence Occasionally ulcerations of the buccal mucous membrane occur A catarrhal inflammation is observed in the eyes the nose and the mucous membranes of the entire respiratory tract

It is rare that a patient succumbs to uncomplicated measles Most commonly death is due to bronchopneumonia which is not due to the measles virus but to a secondary invader chiefly *Streptococcus haemolyticus* The bronchopneumonias are characterized by interstitial reaction and vascular lesions, are often prolonged and may terminate in chronic pulmonary suppurative processes Encephalitis on the other hand is thought

to be due directly to the measles virus Shaffer Rake and Hodes have added credence to this belief by the isolation of the virus from the brain in a fatal case of measles encephalitis The brain in cases of post measles encephalitis shows edema congestion and small petechial hemorrhages scattered throughout both gray and white matter but predominantly in the white matter of the pons medulla and lower cord On microscopic examination perivascular round cell infiltration is seen together with perivascular demyelinization about the venules of the white matter but relatively little destruction of axones or nerve cells

Symptomatology —The *incubation period* is perhaps more constant in measles than in any other common communicable disease Usually ten to eleven days elapse after exposure before the first symptoms appear while fourteen days pass between exposure and the beginning of the eruption Rarely is an incubation period of less than a week observed and only in cases modified by serum is the incubation period likely to exceed fifteen days

The *period of invasion* sometimes called the *period of catarrh* lasts from the onset of symptoms to the appearance of the eruption It is characterized by fever general malaise lacrimation congestion of the conjunctivae catarrhal signs in the upper respiratory passages and congestion of the mucous membranes of the nose and mouth with the appearance in twenty four to thirty six hours of the typical Koplik spots on the buccal mucous membranes A slight defervescence may occur before the appearance of the eruption Variations of the usual temperature curve occur in the natural course of the disease In some cases there is a steady gradual rise in the temperature with the peak reached at the appearance of the rash in others there is an early rapid rise and a sustained temperature until the rash reaches its fullest extent while in the cases modified through the use of serum the temperature curve is usually lower often not exceeding 100° F

Shortly after the onset of the disease the membranes of the eyes become reddened and swollen accompanied by lacrimation and often photophobia A zone of congestion in the lower eyelids described by Stimson, usually gives way in a day or so to congestion involving the entire conjunctiva There is a seropurulent nasal discharge accompanied by attacks of sneezing or hoarseness and a dry, hacking cough which may persist throughout the course of the illness

The *pathognomonic Koplik spots* in the buccal mucosa are found in about 97 per cent of patients Koplik spots appear most often opposite the first molar teeth or deep inside the lower lip as bluish white specks pin point in size surrounded by a bright red areola They are best seen by bright daylight At first there may be only a few but later they become numerous and coalesce to present a moth-eaten appearance on the surface of the buccal mucosa The importance of Koplik spots lies in the possibility of their early recognition which permits the isolation of the patient two to three days before the rash is evident In addition to the specific lesions the mucous membranes are congested and swollen and bluish red blotches often may be seen on the soft palate The catarrhal symptoms in the prodromal stage of measles may be mistaken for those of any form of acute upper respiratory infection Recognition of the disease is possible however through the observation of the conjunctivitis especially the line described by Stimson and the subsequent appearance of Koplik spots A leukopenia with absolute decrease in the lymphocytes is usually present in the blood at this stage

Occasionally in the period of invasion a *prodromal rash* appears often resembling the rose spots of typhoid but more commonly a blotchy erythema similar to mild drug eruptions or to the early erythema of scarlet fever The prodromal rash is transient disappearing before the typical eruption is evident In the period of invasion the spleen may become palpable

The *period of eruption* begins about fourteen days after exposure three to four days after the onset of fever and two to three days after the appearance of Koplik spots The eruption lasts four to five days but may remain as long as a week The eruption is first noted in the hair line behind the ears on the neck and over the forehead It extends from above downward gradually covering the entire body The lesions first

appear as tiny red papules surrounded by pallid areolae They rapidly enlarge to form dusky red macules which increase in number and become grouped together to form blotchy, irregularly shaped lesions which tend to become confluent especially on the face and on the back With the appearance of the eruption the subjective symptoms usually increase and the temperature rises often as high as 104°–105° F The patient complains of itching and burning and his face is puffy his eyes are swollen and red and there is considerable photophobia The discharge from the nose which has been serous often becomes purulent The cough is frequent harsh and unproductive The patient looks and feels miserable After the eruption has reached its peak a striking improvement takes place The temperature drops rapidly the catarrhal symptoms recede the cough diminishes and in a few hours the patient feels much improved The eruption fades in the order of its appearance Desquamation follows in the wake of the rash as a slight brownish scale bran like in character usually completed in five to ten days

Course Modified by Serum —The incubation period of measles modified or attenuated through the use of serum may be prolonged to as much as seventeen or eighteen days The period of invasion may be characterized by a mild catarrhal reaction of the respiratory passages with few subjective symptoms and without the appearance of Koplik spots The eruption appears as transient spotty scattered erythematous lesions often confined to the face and back The febrile response may be sharp but of short duration or may be more prolonged but low grade lasting throughout the period of invasion or eruption At times the febrile rise may be the only manifestation of the disease

Severe forms of measles have been most frequently encountered in debilitated infants and seldom in older patients except among native populations who have been free of the disorder for many years *Hemorrhagic* or *black measles* is a particularly severe form There is marked hyperpyrexia prostration and signs of shock with the appearance of the eruption purpuric spots develop over the entire body Bleeding may occur from the mucous membranes of the nose or pharynx and there may be bloody stools Rarely a highly fatal toxic form of measles is seen with hyperpyrexia cyanosis and delirium, convulsions stupor or coma appearing rapidly after the onset of the disease

Complications —Measles apparently exerts a temporary depressing effect upon immune responses rendering the patient especially susceptible to secondary infections The disease however also temporarily diminishes allergic reactions Consequently although the list of complications of measles is long allergic responses are seldom among them The catarrhal conjunctivitis pharyngitis, laryngitis tracheitis bronchitis and frequently enteritis should be regarded as part of the disease rather than complications Complications are usually those of infection by the streptococcus the pneumococcus the influenza bacillus and occasionally the staphylococcus Infections of the upper respiratory passages the ears paranasal sinuses the larynx and the lungs are most frequent Complications may appear in any stage of measles but are most likely to develop in the late eruptive stage In contagious hospitals diphtheria was at one time frequently encountered as a complication of measles Tuberculous processes may be aggravated by measles resulting in exacerbation and the reappearance of symptoms of a previously quiescent tuberculosis Laryngitis is a troublesome manifestation even in uncomplicated cases of measles but in the presence of secondary infection may be severe and dangerous Hoarseness and a croupy cough are observed in many children with measles while in more severe forms aphonia cyanosis dyspnea substernal and suprasternal retraction may appear The laryngitis usually subsides when the rash begins to fade but if it persists is indicative of secondary laryngeal infection and may require drastic treatment Bronchitis indicated by cough and often by the presence of ronchi is likewise a characteristic feature of the disease If the finer bronchioles are involved signs may persist for some days after the appearance of the eruption Only a longer persistence with continuation of fever or the spread to the smaller bronchioles with appearance of fine crepitant rales should cause anxiety Bronchopneumonia has been the chief cause of

death Though bronchopneumonia may occur at any age it is most frequently a menace in children less than three years of age and in elderly persons

Measles was in 1917 the largest single cause of death in the United States Army, deaths being due mostly to *secondary bronchopneumonia* The bronchopneumonia usually is noted in the late eruptive stage When the eruption has begun to fade the patient does not improve but continues a febrile course with prostration rapid pulse and respiration and frequently a persistent unproductive cough and cyanotic tinge to the lips and nail beds The febrile response is irregular the temperature may be only slightly elevated or it may be swinging or persistently high The physical signs are usually those of a scattered or diffuse pneumonic process characterized by little evidence of gross consolidation but with numerous patches of fine rales throughout both lungs After the process has been present for some time bronchial breathing and impairment of resonance may be observed The disease may run its course in a week or ten days or may be prolonged lasting three to four weeks It is particularly likely to be followed by sequelae such as empyema unresolved pneumonia suppurative pneumonitis interstitial pneumonitis or bronchiectasis Infiltration of the lungs observed on roentgenograms may be a characteristic part of measles and only larger infiltrations which persist after the fading of the rash should be construed as evidence of bronchopneumonia Lobar pneumonia is rarely seen as a complication of measles

Measles seems especially likely to cause an exacerbation of a latent or suppressed *tuberculous process* Consequently tuberculosis should be suspected in patients with prolonged pulmonary signs or with persistent low grade fever or with the appearance of cervical adenitis of prolonged duration Less commonly seen at the present time generalized miliary tuberculosis tuberculosis of the bones and joints and tuberculous meningitis were once common sequelae The tuberculin test during and for a short time after measles may become negative or less positive than it was before the attack

Otitis media accompanied by pain fever redness and bulging of the ear drum is a common complication particularly likely to develop in a hospital ward *Mastoid* disease and *chronic deafness* are less frequently seen after measles than after scarlet fever With individual isolation of each case of measles, the incidence of otitis media may be greatly reduced

Cervical adenitis frequently follows measles but is usually not severe *Catarrhal conjunctivitis* may follow improper care of the eyes and may result in keratitis chronic ulceration or rarely panophthalmitis

Gangrenous *stomatitis* or *noma* is a sequel to measles which is fortunately rare *Cardiac involvement* endocarditis pericarditis myocarditis and other rheumatic manifestations are infrequent

While most of the sequelae of measles are due to secondarily invading organisms the *encephalitis* which follows measles is probably referable to the virus of the disease itself Encephalitis usually develops in the stage of eruption but is often not recognized until the stage of defervescence. The rash fades but the persistence of fever the stupor the muscular rigidity hypertonicity and often generalized convulsions draw attention to the central nervous system Encephalitis occurs in less than one tenth of 1 per cent of cases of measles No apparent relationship exists between the severity of the measles and the development of encephalitis Spinal fluid in measles encephalitis is clear but under increased pressure The cell count may be normal or there may be a pleocytosis as high as two hundred cells mostly lymphocytes There is increased globulin with a normal amount of sugar The *prognosis* of post measles encephalitis is somewhat better as regards life than that of other forms of neurotropic virus encephalitis but the symptoms of coma and stupor may persist for weeks and be followed by permanent sequelae of weakness spasticity tremors ataxia or mental deterioration *Meningitis* of bacterial origin may occur following measles as a sequel to otitis media mastoiditis bronchopneumonia or tuberculosis Scarlet fever diphtheria varicella or pertussis associated with or following measles has been less frequent with the improved care of patients in communicable disease hospitals The frequency of pertussis epidemics following measles may be related to the ordinary sea-

sonal incidence of these two diseases Ordinarily the urine is normal throughout measles although there may be a febrile albuminuria in patients with high temperatures Occasionally nephritis may follow measles but it is a rare complication Gastro intestinal disorders are relatively common and a simple enteritis is particularly troublesome especially in infancy where a diarrheal disorder may lead to a fatal termination

Differential Diagnosis—In the prodromal stages of measles the diagnosis is made with frequency only during epidemics since the catarrhal symptoms are otherwise not enough to suggest the disease The first pathognomonic sign is the appearance of Koplik spots which may not develop until relatively late in the period of invasion They should be sought in bright daylight in the buccal mucous membrane opposite the molar teeth Rarely they fail to appear in patients who have not received serum while in patients who have received serum it is common for Koplik spots to be absent. The diagnosis of measles in the eruptive stage cannot be made from the appearance of the eruption alone since a skin eruption definitely morbilliform may be seen in rubella in roseola infantum in certain cases of serum disease in sulfonamide reactions and in eruptions following the use of phenobarbital dilantin or nirvanol Eruptions following dilantin or phenobarbital medication may closely resemble measles not only in the appearance of the eruption but in the presence of congestion of the mucous membranes The leukopenia present in the pre eruptive stage and the early stage of eruption of measles is of some value However, roseola infantum the drug rashes and serum sickness may be similarly accompanied by a leukopenia

Rubella usually appears with little in the way of prodromal signs the first symptoms occurring within a few hours of the appearance of the rash During the first day German measles may look like a pale measles eruption However the disorder is more often confused with scarlet fever which it resembles on the second day while on the third day the rash usually fades Catarrhal symptoms are minimal and often absent The suboccipital and posterior cervical lymph nodes are characteristically swollen and somewhat tender German measles lasts three or four days and is seldom followed by desquamation or by pigmentation of the skin

A *scarlet fever* eruption on the extremities may present a blotchy appearance suggesting measles but if one examines the trunk as well as the extremities the characteristic scarlatiniform rash is apparent

Serum disease particularly after injection of large doses of unrefined types of serum may be morbilliform in character Careful inspection of the surface of the body usually reveals at least a few urticarial lesions

The eruption of *roseola infantum* (exanthema subitum) resembles quite closely that of measles but is usually a paler pink and is relatively slight on the face The course of roseola should serve to distinguish it from measles Roseola is characterized by three or four days of fever sometimes swinging but often a sustained temperature of 103°-105° F with little prostration and no localized findings with the possible exception of a slight pinkishness of the ear drums and some injection of the buccal mucous membranes Moderate to marked leukopenia occurs in the disease with white counts often as low as 1800 There are no Koplik spots and the temperature usually comes to normal before the rash appears and remains down throughout the period of eruption

Prognosis—The mortality rates of measles have shown in recent years a steady decline apparently paralleling the improvement in general health among infants and children since it was among debilitated undernourished children often those living in institutions that the mortality rate was high Deaths from measles in infants under six months are rare due to the immunity in this age group The death rate reaches its maximum in the preschool years falling rapidly in later childhood Since the deaths are usually due to the complications of bronchopneumonia laryngotracheobronchitis or enteritis it is obvious that crowding or exposure of one measles patient to another may have a definite influence upon prognosis The deaths from measles bronchopneumonia have been strikingly reduced by the introduction of sulfonamide therapy The influence of measles upon tuberculosis

has also been minimized by the diminution of the numbers of cases of childhood tuberculosis Although it is rare for a person to succumb to uncomplicated measles instances of such deaths have occurred particularly *when the eruption is scanty* the temperature extremely high and the patient in a state similar to shock When measles breaks out among populations from which it has been long absent, the disease may be extraordinarily severe and tends to attack individuals regardless of age Thus in the *Faroe Islands in 1846 six* thousand persons out of a population of 7 782 were attacked and it is estimated that about a quarter of the population died within three months The Territory of Hawaii experienced in 1936–1937 the most virulent epidemic of measles in its recorded history This *epidemic* began in November 1936 and lasted until December 1937 The incidence equalled that of the preceding twenty years and was accompanied by a high mortality Such epidemics have seldom been encountered in the continental United States In 1940 the case fatality rate of measles in the *United States* registration area was about 0.2 per cent Even the reported death rate may give an exaggerated picture of the dangers of the disease inasmuch as the actual incidence of measles has been estimated to be two to three times the number of cases reported

Prophylaxis—The public health measures employed for the control of communicable diseases such as reporting of cases placarding of homes and isolation of patients have been inadequate to prevent the spread of measles Infectivity begins with the onset of symptoms or shortly before and persists probably *until* the peak of the eruption is reached Communicability is thus probably greatest before the appearance of the rash It is to be emphasized that measles patients apparently will not spread measles after the rash has faded In most communities isolation of patients is required for four or five days after the appearance of the eruption or until the eruption has faded Exposed children who have been in intimate or direct contact with a patient should be kept under quarantine beginning eight or nine days after the first *known* contact and continuing until fifteen days after contact has ceased If serum is administered for the modification of the disease quarantine of the contact should be continued until eighteen days after the last exposure In a ward of susceptible children where the onset *and duration* of contact can be established it is safe to keep the ward open for one full week before the *isolation of the exposees* is necessary Although 95 per cent or more of the population sooner or later acquire measles unnecessary exposure should be avoided particularly of older infants and children of preschool age The importance of isolation of patients with measles is less perhaps *in the prevention* of the spread of the disease than in minimizing the incidence of secondary infection

No satisfactory means of *active immunization* against measles has been developed The studies of Shaffer Rake and Stokes must be considered as encouraging but successful *repetition of these trials* is needed Until the material for active immunization or for the production of the attenuated disease by a modified or attenuated virus shall have been further tested the prevention or modification of the disease by the use of human immune bodies remains the most effective *means of prophylaxis* With complications occurring less frequently and in the presence of a steadily declining death rate fewer indications exist for the use of serum in prevention or modification of measles Antibodies against measles are found in the blood of almost all patients who have recovered *from the disease* The antibodies are probably of highest titer in fresh convalescent serum but apparently persist in protective quantities throughout life possibly augmented by re-exposures Since no *small* laboratory animal is readily susceptible to measles an adequate means of titering the antibodies has not been devised In 1923 Debre described a test for the inhibition of the rash in measles by intracutaneous injection of serum Unlike the Schultz Charlton blanching test in scarlet fever the *measles serum had to be* introduced before the rash developed in the area of injection Fresh convalescent serum even in 2 per cent solution may produce the Debré phenomenon whereas adult immune serum *and placental* extracts are seldom effective in solutions weaker than 5 per cent

Convalescent serum adult immune serum and *immune globulin* derived from the human placenta may all be effective in the prevention or modification of measles Three to 6 cc of blood serum of convalescent patients (blood taken a week or more after the disappearance of the measles eruption) injected subcutaneously or intramuscularly into the exposed child within four days after exposure usually gives complete protection This immunity however is passive in character lasts but a few weeks and usually suffices to cover only the one exposure If adult immune serum is used 15 to 20 cc are required The effective dose of immune globulin varies from 2 to 4 cc depending upon the preparation employed If antibody

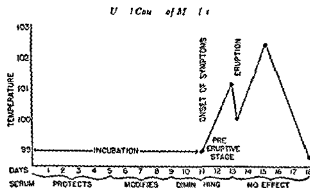


Fig 3—The effect of convalescent serum adult immune serum or immune globulin (placental extract) on the usual course of measles

is given as late as the sixth or eighth day after exposure protection usually does not ensue but the disease may be ameliorated to a modified or attenuated type The incubation period may be prolonged to as much as seventeen to eighteen days The severity of the disease is reduced and complications are less frequent yet the attenuated attack usually results in a permanent immunity The treatment of measles during the pre eruptive stage by convalescent serum in dosages of 40–50 cc by intravenous injection has been advocated Amelioration of the severity of the symptoms can often be obtained up to the appearance of the eruption but later use of the serum is without effect Local reactions are frequently encountered following the use of placental extract but seldom following the injection of convalescent serum or adult immune serum

Treatment —While chemotherapy has not developed a drug effective against measles further reduction of an already low death rate has been achieved through the use of sulfonamide compounds in the treatment of the bacterial complications

Rest in bed adequate food and fluids care of the bowels protection of the eyes, emollient applications to the nose and sedatives to counteract cough are usually the only therapy required in uncomplicated measles The room occupied by a measles patient should be well ventilated and kept warm Cold air seems to irritate further the mucous membranes affected by the disease Should symptoms of tracheitis or bronchitis be distressing higher temperature and increased humidity may add to the comfort of the patient In severe cases of laryngitis croup tents with steam inhalations may give relief The eyes usually need no protection other than that obtained by avoidance of bright light The short duration of the disease renders the problem of nourishment of minor importance

Antipyretic treatment may be necessary when the temperature becomes high but usually only if the pyrexia is accompanied by nervous symptoms such as restlessness stupor delirium or convulsions Coal tar antipyretics such as phenacetin or antipyrene are usually effective but warm alcohol or tepid water sponges are preferable Acetylsalicylic acid in doses of 5 to 10 grains may achieve the same results The fall in temperature is usually accompanied by a marked diminution of systemic symptoms Convulsions which sometimes occur at the onset of a febrile illness in children may be observed at the onset of measles Usually treatment for the pyrexia results in the cessation of convulsions Occasionally phenobarbital or paraldehyde may be necessary to control the attack

Sulfonamide compounds have been found to be effective in the treatment of the bacterial complications particularly those due to the streptococcus or pneumococcus Sulfathiazole or sulfadiazine seem at present the preparations of choice since they have a wide bacterial coverage and are well borne by infants and children The dosage should be approximately 1 0 grain (0 065 Gm) per pound of body weight per day for a child up to five or seven years of age Since the

greatest dangers of measles are due to the development of complications sulfonamides may be given prophylactically to a child during the attack of measles if he has been acutely or chronically ill preceding the onset of the disease With the advent of chemo therapy, most of the symptomatic procedures used in the treatment of postmeasles bronchopneumonia have become of secondary importance However occasionally the bronchopneumonia is of nonbacterial origin possibly of the so called virus or atypical type Under such circumstances only symptomatic treatment is available In these cases the temperature is usually not high but the respirations are rapid and the physical signs diffuse and accompanied by considerable cyanosis The position of the patient should be changed frequently to prevent pulmonary congestion Sedatives should be used sparingly so that the cough will be relieved but not inhibited as coughing or deep breathing and crying apparently minimize occlusion of the smaller bronchi An oxygen tent may become necessary in some cases

Otitis media in measles may give rise to serious complications Frequent changes of the patient s position in bed are thought to help prevent the incidence of otitis *Paracentesis* of the tympanic membrane is not recommended except in the presence of persistent pain together with bulging of the ear drum Relief of pain is prompt with paracentesis although pus may not be discharged until several hours later Many of the cases of otitis media in infancy and childhood clear up without the development of suppuration especially if sulfonamide drugs are used in therapy Dry wipes of the discharging ear are usually all that is necessary Wicks in the ear are not desirable nor are irrigations necessary unless the purulent discharge becomes thick and occludes the canal

There is no satisfactory treatment for *measles encephalitis* Patients may be kept quiet by sedation with phenobarbital paraldehyde or in very severe convulsive cases by avertin

In *convalescence* from measles the child s activity should be restricted until his strength has returned Most important in the treatment of measles is the attempt to prevent secondary respiratory involvement Attendants upon patients with measles should wear an outer garment which can be removed before contact is established with the rest of the family The hands should be scrubbed thoroughly on leaving the room occupied by the patient Because of the susceptibility of measles patients to bacterial respiratory infection masking of the attending personnel is indicated The dishes and linen of the patient should be boiled after each use The heavier bedding such as blankets and mattress and the whole room should be aired thoroughly when the disease has subsided

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RUBELLA

(*German Measles Rotheln*)

Definition —Rubella is an acute specific epidemic and highly contagious disease similar to but quite distinct from measles and scarlet fever It is characterized by a long incubation period short invasive stage benign course and almost complete freedom from complications

Etiology—Although the *specific agent* has not been definitely isolated it is probably a filtrable virus which is present in the buccal and nasal secretions The disease is transmitted chiefly if not entirely by direct contact The possibility of infection through fomites or a third person has not been determined The infectivity is less than that of measles and of short duration Like measles rubella is infectious for only a day or two before the eruption appears

Rubella is prevalent during the first half of the year The *incidence* begins to rise during January becomes maximal in May and June, and then falls abruptly The characteristic local outbreaks occur among aggregations of unprotected individuals Although children between the ages of three and twelve years are most susceptible young adults who have not had the disease during childhood are frequently attacked Children who had measles develop rubella more often than children who had not Infants under six months of age have a certain degree of immunity One attack almost invariably protects against others but not against measles or scarlet fever Every three or four years a more or less pronounced epidemic occurs and occasionally an outbreak of severe rubella resembling measles is reported

Symptoms—The period of *incubation* varies from ten to twenty two days but is usually seventeen or eighteen days A short period of pharyngeal catarrh usually precedes the rash by about twenty four hours Rarely a longer prodromal period of ill defined discomfort occurs before the eruption appears The characteristic adenitis of the mastoid occipital and cervical glands can in the majority of cases be detected a day or two before the appearance of the rash

The *rash* is papular and morbilliform in the beginning but frequently becomes scarlatiniform in the second stage It appears as discrete round or oval spots first on the face or neck around the mouth or behind the ears and occasionally on the scalp Sometimes the wrists chest shoulders or even the legs are affected first The rash which spreads rapidly downward may cover the entire body in the course of a day In most cases it fades as rapidly as it develops so that the face is almost clear by the time the lower extremities are involved The papules which are smaller than those of measles are pink in color and tend to cluster in small groups The rash may be scarlatiniform on the second day This is most marked on the trunk, especially on the back The rash rarely persists more than seventy two hours and hardly stains the skin contrasting in this respect with measles It may be followed by a three day desquamation

The mucous membrane of the *mouth* is not inflamed and Koplik's spots never occur Fine vesiculation and congestion of the soft palate are often seen The tonsils may be slightly swollen and reddened and there may be some pharyngeal catarrh The *conjunctivae* are pink and the eyes slightly suffused Photophobia is rare The *temperature* usually rises as the rash appears but rarely exceeds 101° F The increase seldom lasts longer than two or three days Often there is no fever at all

The *adenitis* which is very distinctive involves the mastoids occipital posterior cervical and frequently the axillary and inguinal glands These usually become enlarged to the size of small peas and are firm discrete and tender They resolve rapidly without suppuration when the rash subsides The blood undergoes no characteristic changes

Convalescence is rapid A slight furfuraceous desquamation may occur

Complications and sequelae are rare and trivial although otitis arthritis nephritis endocarditis and encephalitis or meningoencephalitis have been reported occurring chiefly in severe epidemics Encephalitis occurs less frequently than after measles the patients appearing dangerously ill but usually recovering quickly and completely Mild recurrent sore throat slight laryngitis slight bronchial catarrh mild rheumatic pains or transient albuminuria are those more commonly observed

Diagnosis—Rubella is confused chiefly with the mild forms of measles and scarlet fever especially when it is severe *Measles* can be differentiated by the shorter incubation period of fourteen days by the marked catarrhal symptoms the presence of Koplik s spots a more severe constitutional reaction and the rash which is darker and more persistent and stains the skin *Scarlet fever* has an even shorter incubation period

(about seven days) and is characterized by initial vomiting headache, and high fever, and the absence of rash upon the face Rashes caused by toxins and drugs are usually polymorphic and irregularly distributed They are not accompanied by the glandular enlargement characteristic of rubella *Erythema scarlatiniforme* bears a greater resemblance to scarlet fever than to rubella it avoids the face does not cause enlargement of the mastoid or occipital glands and tends to recur *Pityriasis rosea* which is perhaps an infective fever may be distinguished by the so called Herald patch which precedes the general eruption, as well as by the usual primary localization on the upper part of the trunk In this disease the patches are scaly often macular and ringed The papules which are decidedly larger and more persistent than those of rubella desquamate characteristically from the center toward the margin *Secondary syphilids* bear a superficial resemblance to the rash of rubella but may be easily differentiated

Prognosis.—Recovery is the rule Although rubella is known to recur second attacks are not common Relapses occur very rarely

Treatment.—*Prophylactic*.—Exposed individuals should be isolated from the tenth to the twenty first day after exposure to the infection A careful watch should be kept for tenderness and swelling of the mastoid and occipital glands Pooled human serum or plasma is effective in the control of epidemics and if used more generally would reduce markedly the incidence of this disease

Therapeutic.—The patient should be isolated and kept in bed until all symptoms have subsided If no complications develop quarantine may stop after seven days although the Association of Medical Officers of Schools advises that it continue for ten days

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HERPES SIMPLEX

(Herpes Febrilis Symptomatic Herpes Fever Blisters Cold Sores)

Definition.—Herpes simplex is an acute infectious disease of man characterized by groups of superficial watery blisters in the skin or mucous membranes The malady is transmissible to lower animals particularly rabbits

Etiology.—Löwenstein and Grüter showed that an infectious agent is the cause of herpes simplex Since the reports of their work ample evidence has been adduced to justify the classification of the agent, possessing a diameter of 100 to 150 millimicrons with the filtrable viruses Doerr and Vöchting and many others have shown that this virus is also capable of attacking the central nervous system of experimental animals

Incidence.—Some herpetic eruptions appear without apparent association with other pathologic conditions others are secondary to, or are associated with such diseases as malaria pneumonia and cerebrospinal meningitis still others *e g* menstrual herpes recur at the same spot at regular intervals Injections of foreign proteins *e g* vaccines or fever therapy frequently precipitate an attack of herpes

Symptoms.—The lesions may occur anywhere in the skin of the body including the genitalia in the conjunctiva and in the cornea At times particularly in the skin of the face the distribution is similar to that of zoster lesions and in these instances the virus can be recovered from the nerves or ganglia supplying the affected area The lesions first appear as painful swellings which quickly develop into watery blisters surrounded by areas of erythema The symptoms caused by herpetic infection except the local lesions are not clearly defined because

the malady usually accompanies other diseases Some observers however hold that an uncomplicated herpetic infection may produce chills fever, headache malaise, and anorexia which disappear in two or three days

Pathology —Hyperplasia of epithelial cells which then are destroyed to form vesicles and the development of inflammation in the corium are the changes observed in affected tissues Nuclear inclusions characteristic of many virus diseases are seen in infected cells

Prognosis —Unless a secondary infection occurs recovery is the rule but one attack does not protect against subsequent ones

Treatment —After the appearance of lesions treatment should be symptomatic Tanning of the skin which is subject to recurrent attacks of herpes seems to lessen their number and severity

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HERPES ZOSTER

(Shingles Zona Zoster)

Definition —An acute specific infectious disease characterized by inflammation of one or more dorsal root ganglia or the extramedullary ganglia of the cranial nerves and accompanied by an eruption of irregularly outlined groups of vesicles distributed along the course of the corresponding peripheral sensory nerve

History —This disease long known as a clinical entity and named by the Greeks zona was first shown to be related to inflammation of the corresponding dorsal root ganglion by Barensprung in 1863 The classical paper of Head and Campbell (1900) gave a firm foundation of its neuropathology and Lipschutz in 1921 defined the specific features of the cutaneous vesicular lesion Bokay s observations (1909) indicated its possible etiologic relation to varicella those of Teague and Goodpasture (1921) pointed out its similarity to certain lesions of herpes simplex and Kundratitz (1925) first reported successful experimental inoculations into human subjects Others have failed to transmit the infection experimentally

Etiology —Evidence of the infectious nature of herpes zoster is afforded by such clinical manifestations as variable systemic disturbances fever and subsequent immunity by its epidemiologic features of occasional epidemic outbreaks and seasonal incidence by the specific cytologic characteristics of its cutaneous lesions and by reported successes in experimental transmission to human subjects

More specifically evidence indicates also that the disease is due to a filtrable virus although the virus has neither been definitely demonstrated by experimental transmission in series nor consequently filtered The most direct indications that the active agent is a virus are the presence of acidophilic *intranuclear inclusions in cells of the* cutaneous eruption its contagiousness reported successes in transmission and the manifestations of active immunity following an attack

Morbid Anatomy —The classical studies of Head and Campbell demonstrated that the basic lesion of the manifest disease is located in one or more dorsal root ganglia or the gasserian ganglion corresponding to the sensory nerve distribution to the areas of eruption They showed that the changes in the dorsal root ganglion are situated in its dorsal aspect *i e* in that portion opposed to the anterior root and in the acute stage consist of severe inflammation with exudation of small round deeply staining cells extravasation of blood destruction of ganglion cells and fibers and inflammation of the sheath of the ganglion

These changes are followed by acute de

generation in the peripheral nerve in the posterior nerve root and in corresponding fibers of the spinal cord The inflammatory focus in the ganglion on healing becomes transformed into a fibrous scar depending in its size and density upon the extent of the original inflammation but usually occupying from one sixth to one half of the ganglion All the ganglion cells and nerve fibers within the scar are destroyed The sheath over the scar is thickened If the inflammation is mild the ganglion may be left apparently normal In rare cases paralysis of local muscles indicates involvement of the fibers or neurons of the anterior horns

The cutaneous vesicle rising from an erythematous base is situated in the epithelial layer and its floor is formed of naked papillae There is marked inflammation of the corium at the base with congestion edema and infiltration by mononuclear cells The vesicle may be divided into compartments by septa which are remains of incompletely separated epithelial layers retaining their attachments The yellowish fluid within the vesicle is either clear or slightly cloudy from the presence of desquamated epithelium and inflammatory mononuclear cells

Acidophilic intranuclear inclusions especially numerous in earlier stages are found in epithelial cells about the vesicle They occur also in the connective tissue cells in the adjacent corium These inclusions first described by Lipschutz constitute the specific element in the lesion and indicate the activity of a virus No similar inclusions have been described in the cells of the affected ganglion and if present they would be demonstrable probably only in the earliest stages of the lesion

Nothing is definitely known about the portal of entry of the suspected virus although the rather frequent occurrence of cases of so called symptomatic herpes zoster secondary to ome irritating or injurious lesion about the ganglia such as tuberculosis syphilis or tumor indicates that it may be commonly present in the environment or perhaps often latent in the human tissues

Head and Campbell showed in their analysis of over 400 cases that the dorsal ganglia most frequently affected are those that receive afferent fibers from the viscera through the white ramus of the sympathetic branches This fact in view of the present hypothesis of spread of certain neurotropic viruses along axons at least suggests the possibility of initial peripheral foci of infection with secondary localization within a ganglion followed by injury and necrosis of its cells accompanied by hemorrhage and inflammation Virus liberated from infected neurons presumably extends centrifugally to localize in cutaneous epithelial cells in contact with the corresponding peripheral terminations of nervous filaments As a consequence of degeneration and necrosis of these cells the vesicle with its attendant inflammatory phenomena appears The probability of such a course of events is suggested by the experiments of Teague and Goodpasture with the virus of herpes simplex which if inoculated into the tarred skin of rabbits or guinea pigs will cause a specific ganglionitis and zosteriform eruption quite similar to that of herpes zoster in man

Signs and Symptoms—In cases of so-called essential or idiopathic herpes zoster a typical attack arises without any obvious peripheral or central cause There is a prodromal period usually of three or four days duration during which the patient feels ill the temperature is elevated and there is more or less pain At this time a definite diagnosis cannot be made but suddenly the erythematous and vesicular eruption appears with its characteristic distribution along the course of a nerve usually of the trunk occasionally in a trigeminal area There is often an increase in the number of cells in the spinal fluid

The febrile period lasts usually from three to five days and with its subsidence drying and healing of the cutaneous lesions take place Secondary infection may delay healing and increase the tendency to scarring Neuralgic pains may persist especially in elderly people and rarely there is some local residual paralysis

Herpes zoster of the face is not uncommon and is often severe It involves the first branch of the sensory division of the trigeminal nerve and may lead to severe corneal ulceration which requires special care The other cranial nerves are rarely affected

Diagnosis—Because of the characteristic nervous distribution of the cutaneous vesicular eruption the diagnosis is usually not

difficult after the rash appears In children and rarely in adults the local eruption may be followed by the appearance of more or less generalized vesicles unrelated apparently to cutaneous innervation In such cases of a generalized vesicular exanthem there may be a question, especially in children, whether or not the disease is in reality varicella Indeed there is considerable clinical and epidemiologic evidence that the two viruses, that is those of herpes zoster and of chickenpox are the same or very closely related etiologic agents The histopathology of the cutaneous lesions offers no distinction between the two for as was shown by Tyzzer in 1906, acidophilic intranuclear inclusions occur in the epithelial cells about the vesicles and in the corium of cutaneous lesions of varicella, and these, as well as other elements of the inflamed skin are similar to those of herpes zoster

Occasionally the virus of herpes simplex causes a vesicular eruption along the course of a cutaneous nerve usually quite limited in extent and it may involve the supra orbital branch of the ophthalmic nerve This may simulate a mild herpes zoster very closely The presence of the virus of herpes simplex can be determined, however by inoculating vesicular contents into the scarified cornea of a rabbit Herpes simplex virus is very infectious for the rabbit and if present in the test a profound herpetic keratitis not infrequently followed by encephalitis will ensue The viruses of herpes zoster and of varicella on the other hand have never been proved to be successfully inoculable into other than the human host

Treatment —There is no specific treatment for the infection Alleviation of irritation and pain and prevention or care of secondary infection are the indications for therapy in the essential variety In some cases of the symptomatic type which may recur treatment of the associated disease or local lesion may be helpful as for example of cerebrospinal syphilis which is not infrequently accompanied by herpes zoster

According to Kraus the pain in the acute stages should be relieved by codeine in ½-grain doses given every four hours The skin lesions may be covered with collodion If ruptured an ointment of 1 per cent cocaine in lanolin is advisable Recently deep x ray therapy has become a popular method of treating herpes zoster The dosage is 200 to 250 R U a day for five or six days directly over the dorsal ganglia involved The best results are obtained when roentgen therapy is used early in the course of the disease, that is during the first two to three days Subcutaneous injections of pitressin have been advocated by some but there is no rationale for such a treatment and the results are disappointing

The post herpetic neuralgia may be very refractory to treatment Aspirin pyramidon and codeine may be used for the relief of pain Cobra venom has also been tried with some success Severe intractable root pain occasionally has to be treated by posterior root section

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VARICELLA

(Chickenpox)

Varicella is a mild communicable disease of childhood characterized by fever and a vesicular eruption with erythema around the vesicles involving the skin over the entire body and the mucous membranes of the mouth and throat

Etiology —The causative agent of varicella has not been identified but probably like other pox infections it is due to a virus A striking characteristic of varicella in which it resembles measles is the highly communicable nature of the virus which appears to spread chiefly by the air borne route

although direct contact and droplet "hits" from sneezing coughing or speaking at times must play an important role The virus apparently enters through the respiratory tract and is spread by the same route during the early catarrhal stages of the disease when mild inflammatory reactions of the mucous membranes of the nasopharynx are more evident Spread of the disease also occurs from the vesicles on the skin during the early stages of the eruption but probably no spread of the virus occurs after the appearance of crusts The virus has not been grown successfully on the chick embryo or its membranes as yet and other animals than man do not appear to be susceptible A close relationship may exist between the virus of varicella and that of herpes zoster in that epidemics of varicella are associated with attacks of herpes zoster and herpes zoster has been said to incite epidemics of varicella or to be associated with their inception Although there may be a certain degree of cross immunity existing between varicella and herpes zoster accurate determination of their relationship cannot be made until satisfactory methods for identification of the virus of varicella are developed

Immunity is usually permanent following a single attack Transplacental passive immunity may be present in newborn infants although cases have been recorded in infants within the first two weeks of life The rarity of exposure of newborn infants to varicella has delayed conclusive evidence on this question

Incubation —The incubation period usually is fourteen to sixteen days but in many instances the first symptoms and signs occur as late as twenty-one days from the time of exposure

Symptoms and Signs —Prodromal symptoms may be severe particularly in adults but in childhood they are apt to be mild or absent with nasopharyngitis mild fever headache malaise and anorexia Within twenty four to forty eight hours crops of papules and later of vesicles begin to appear on the face and trunk particularly about the shoulders and usually a few appear on the buccal mucosa or pharynx The large majority of lesions are vesicular The vesicles are slightly elevated with a surrounding circular erythema or areola and it is difficult to mistake them for any other lesion except possibly those of variola In variola however in addition to the severity of the symptoms and the more extensive character of the rash the vesicles appear almost simultaneously and are usually larger with a greater tendency to umbilication

In varicella the appearance of fresh crops of vesicles in the same area of skin over a period of twenty four to seventy two hours is characteristic and for this reason in contrast to variola the lesions are usually seen in various stages of development some as small translucent vesicles some with slight umbilication as the vesicles dry from the center, and some with dry firmly attached crusts Also in variola the severe symptoms precede the eruption while in varicella the symptoms accompany the eruption unless the disease is unusually severe Severe irritation and itching usually accompany vesiculation in varicella and for this reason in younger children the larger lesions are rarely permitted to heal "by first intention" unless care is taken to prevent scratching and to relieve the severe itching Excoriated areas and larger crusts are the inevitable result

On the buccal mucosa or the pharynx the vesicles early become small ulcer craters with a surrounding erythema and resemble closely the type of ulcer so frequently seen in herpetic stomatitis Two particularly annoying points of attack are the larynx and the conjunctivae At times vesicles in these structures may be dangerous because of complicating bacterial infections The genitalia also must be examined daily since lesions on these areas are often scratched and secondarily infected Another area frequently overlooked is the scalp where the matting of hair over scratched and crusted lesions results in severe secondary bacterial infections with enlarged and tender occipital and posterior cervical lymph nodes

In the mildest cases only ten to twenty lesions may appear on the skin and there may be no fever or only a transient fever of a few hours in the more severe cases the discrete vesicles will dot the entire body surface and the temperature rises to 103° or 104° F for several days at the time of the appearance of the rash The disease in adults may at times be dangerously severe

before and during the appearance of the eruption Rarely, *necrosis occurs around* the vesicles resulting, if widespread in lesions which have been termed varicella gangrenosa

Complications —The most severe complications may occur in those children who are subject to eczema or staphylococcic infections of the skin In such children the vesicles rapidly fill with pus and are usually ruptured by scratching, with a resultant spread of infection and ulceration Such ulceration and crusting are typical of impetigo contagiosa and many cases of varicella observed first in the late stages would be diagnosed as impetigo were a proper history not available Following the usual case of severe varicella, a few small scars or pox marks remain about the face or shoulders even though scratching has been avoided but in the secondarily infected case with pus and crusting the pox marks may be large and disfiguring Hemolytic streptococci resulting in severe cellulitis and erysipelas have been less common secondary invaders but, until the advent of the sulfonamide drugs, they were the complicating organisms most feared A small percentage of cases of acute glomerular nephritis are the result of skin infections, and varicella with its complications plays an important role in this group of causative factors Pneumonia from laryngeal ulceration abscesses of lymph glands draining secondarily infected areas and serious eye infections are other less common complications to be avoided by proper preventive measures

A rather infrequent but important complication due probably to the activity of the virus only is encephalitis which is similar to that caused by measles and by other communicable diseases It occurs in the more severe cases of varicella usually toward the end of the febrile period but may at times appear one to three weeks following the attack of the disease It is rarely fatal and complete recovery usually occurs

Diagnosis —The appearance of vesicles on the skin each surrounded by a ring of *erythema and* accompanied by a fever however slight is the *sine qua non* of varicella If the disease is seen in this stage of vesiculation and when the crops of eruption in the various stages of translucent vesicles vesi

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which may reach the height of 106° or 107° F In children convulsions and vomiting or drowsiness quickly followed by coma may occur The patient is usually prostrated the face is flushed the pulse is usually full and bounding and marked restlessness which at times amounts to delirium supervenes

Transient rashes resembling scarlet fever or measles may occur during the *prodromal stages* of the disease while the temperature is approaching or when it has reached its highest point Such rashes occur only during the first two days and are found usually over the lower abdomen and the inner aspects of the thighs The position of the rash and its lack of elevation serve to distinguish it from measles or scarlet fever At times such a rash initiates the more severe types of smallpox

On the third or fourth day, *raised macules* begin to appear over the face The earlier these macules appear, the more likely is the rash to become confluent The macules rapidly develop into *papules* and with this development there is associated an immediate diminution in the severity of symptoms and the fever the patient becoming considerably more comfortable The fever and symptoms may increase again later with the multiplication of staphylococci or streptococci in the pustules with their attendant complications The single crop of papules are firm and shotty 2 to 4 mm in diameter with an appearance unlike any other exanthematous disease Widespread tuberculids all of the same size and symmetrically distributed could have the same appearance With the increasing size and tenderness of the papules *multilocular vesicles* begin to form over the papules on about the sixth day characteristically umbilicated due to a dry and depressed center Some vesicles are superficial while others are deeper and not so readily recognized By approximately the eighth day the vesicle becomes full of cloudy fluid and the typical *pustular rash* is in full bloom The pustular nature of the lesion apparently is not dependent upon the presence of secondarily invading bacteria although they are usually present and greatly increase the danger of complications The pustules are slightly larger than the papules with somewhat greater elevation and have a very characteristic greenish or grayish yellow color A small red areola forms about each lesion at the time of vesiculation a phenomenon which occurs synchronously with the development of an allergic response of the skin to variolous material

Although the lesions may vary slightly in size they proceed through each stage of development at the same time—do not appear in crops as is characteristic of varicella with which otherwise mild smallpox might be readily confused While all of the lesions appear at approximately the same time a small percentage of them do not progress through all of the characteristic steps but remain at times only as papules or with very slight evidence of vesiculation In such lesions involution occurs frequently in the earlier stage of the disease

The rash usually appears on the face and about the wrists only slightly in advance of its appearance on the rest of the body and then rather rapidly involves the rest of the forearms upper arms and thorax The abdomen and legs are often only slightly involved but in severe cases this may not be true Such severe cases in which the rash is widespread and where the lesions are so closely studded over the skin that they coalesce are termed *confluent* smallpox; whereas in the absence of coalescence the term *discrete* smallpox may be used

Frequently these two forms confluent and discrete occur in the same patient the confluent lesions appearing on the face and about the wrists while the discrete lesions appear on the thorax abdomen and legs In certain confluent lesions the area involved has almost the appearance of a large abscess On the face these lesions can be particularly distressing often producing extreme discomfort edema may close the eyelids and involve the tissues of the neck as well Edema of the hands and feet often occurs in children At the height of the pustulation lesions frequently occur in areas which must be watched closely for secondary infection the mouth and nasopharynx the prepuce, the labia and the vagina Lesions on the palms and plantar surfaces are not apt to develop into vesicles and pustules but nevertheless form crusts Marked pitting of the face or arms occurs as a rule only in the confluent form of the disease

With the appearance of pustules in the more severe cases, the temperature which has fallen with the earlier appearance of the papules again begins to rise and subsides only when satisfactory crusting has occurred Staphylococcic and streptococcic invasions of the pustules apparently are chiefly responsible for the secondary febrile reaction The pustules and crusts itch severely and scratching must be prevented Desquamation may begin at the twelfth to the fourteenth day and unlike the branny desquamation of measles and scarlet fever the desquamating crusts are thick and brownish yellow in appearance A dark blue dis-



Fig 5—Smallpox in an unvaccinated child showing distribution of eruption



Fig 6—Same patient as Fig 5 showing eruption on back and palms

(Reprinted from the article of Dr Murray Cowie in the 5th edition of Cecil's Textbook of Medicine)

coloration of the skin occurs in the area from which the crust has separated but this gradually and completely disappears

Blood—There is usually a leukopenia together with a relative mononucleosis in the earlier stages of the disease but later a leukocytosis occurs particularly during the pustular stage and when secondary complications occur Anemia usually occurs together with enlargement of both the spleen and the liver In the two hemorrhagic types of smallpox previously mentioned considerable depression of the bone marrow and the liver may occur resulting apparently in alterations in the platelets fibrinogen and prothrombin The exact origin of such hemorrhagic phenomena however is not entirely clear

Varioloid—This term is usually applied to smallpox modified by a vaccination which has 'taken' successfully within approximately five years The lesions are of the discrete type the prodromal symptoms are rarely severe there is no secondary rise of fever and the lesions frequently undergo involution with a markedly shortened course

Abortive Types—Occasionally in recently vaccinated individuals early involution of the eruption occurs even before vesicles are well established and in rare instances the eruption never develops a condition which is known as *variola sine eruptione*

Complications—The common complications of smallpox may be considered as largely due to the secondary invasions of staphylococci and streptococci Abscesses septicemia nephritis erysipelas laryngitis and the various lower respiratory infections can usually be traced to these organisms together with, at times the pneumococcus Corneal ulcers and pustules of the eyelids are not uncommon Rarer though still important complications are diarrhea and otitis media in children while in adults the rare complications are hemiplegia enceph

alitis polyneuritis decubitus ulcers and gangrene

Diagnosis —Difficulties in diagnosis arise chiefly from the following conditions

Varioloid with the involution of many of the lesions can be confused at times with varicella In such cases one must depend upon the appearance of varicella in crops of lesions in all stages of development and also upon the difference in distribution of varicella which is more plentiful on the trunk

The *severe hemorrhagic forms* can be confused with septicemia or severe meningococcal infection Blood cultures should establish the diagnosis

The *initial rash* which occurs in severe forms may be confused with measles or scarlet fever The short duration of the early evanescent rash of smallpox and the other accompanying symptoms should assist in differentiation

Pustular syphilids are at times extremely difficult to differentiate from smallpox In certain instances one can depend only upon the history and the Wassermann reaction for differentiation

The injection intradermally of heat killed vaccine virus may be used also as a diagnostic test for smallpox after the vesicles have appeared or the contents of the vesicles may be used in a similar manner If positive for smallpox a local reaction occurs at the site of injection within a few hours and reaches its maximum within approximately twenty four hours If the patient has been vaccinated previously this test is not significant A similar test has utilized rabbits sensitized to cowpox vaccine and the vesicular contents The vesicular contents have also been used as antigen in a complement fixation test with serum from sensitized rabbits

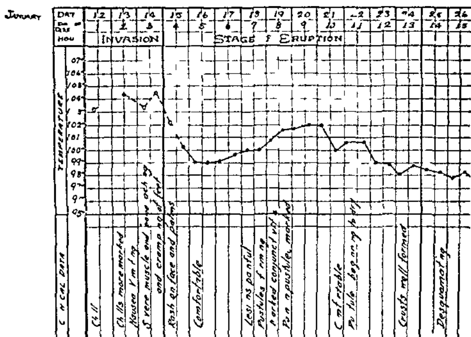


Fig 7—Typical temperature curve from a case of smallpox illustrating the secondary rise (Reprinted from Dr Murray Cowie s article in the 5th edition of Cecil s Textbook of Medicine)

The use of rabbits limits the availability of the latter tests but the intradermal injection of heat killed vaccine virus may be of assistance in difficult diagnostic problems

Prognosis —The prognosis in smallpox depends largely upon the severity of the particular case In the epidemics of recent years the mortality has been distinctly lower than in the prevaccination era The cases accompanied by high fever are more likely to be fatal Complications particularly those in the respiratory tract add to the seriousness of the prognosis

Prophylaxis —The problem of vaccination is considered properly under the chap

ter on Vaccinia Emphasis must be placed upon the fact that vaccination even during the incubation period of the disease may prevent its development Strict quarantine is essential

The disease at times is air borne as well as being transmitted by contact or by direct droplet "hits" from the patient's nasopharyngeal secretions and means of sterilization of the air, if practicable must be considered as well as the prevention of close contacts and of spread by fomites

Treatment —The principal consideration in the treatment of smallpox is the prevention of secondary infection of the vesicles and pustules The secondary elevation of temperature which usually follows the appearance of the vesicles and pustules is probably dependent upon the bacterial invasion of the lesions, and particularly by staphylococci and streptococci Treatment therefore should be aimed essentially as in varicella, toward the prevention of itching and the cleansing of fingers the skin and garments or clothing which may come in contact with the lesions Also scrupulous care must be taken by those caring for the patient The advent of the sulfonamide drugs and recently also antibiotic preparations such as penicillin or penatin should assist greatly in the local treatment of the lesions of smallpox Swabbing the lesions in wet dressings of potassium permanganate 1 4000 may prevent serious infection A 20 per cent sulfonamide suspension in water or similar suspensions appear preferable to sulfonamide ointments due to crusting but it is important that crusts should not be removed too quickly in view of the possible resultant scarring Bathing the lesions gently with hot water or antipruritic lotions should be done to alleviate the itching although here also the sulfonamide preparations are of assistance

Dehydration is a frequent severe complication of smallpox and should be avoided by rectal intravenous or hypodermic fluids particularly glucose if vomiting occurs The possible benefit of convalescent serum has not as yet been determined The isolation period should be at least fourteen days and longer if the lesions remain in an active stage

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VACCINIA

Vaccination or active immunization against smallpox by means of the virus of cowpox is the first procedure of this type known to medicine and its discovery and development by Jenner long before bacteria or viruses had been identified is one of the most dramatic events of medical history The antigenic serologic or possible morphologic relationships between the viruses of cowpox and smallpox are not understood as yet although in view of the proved immunity produced by vaccination with the cowpox virus against smallpox these relationships must be very close

The virus of cowpox has been ordinarily preserved by glycerination of lymph from inoculated calves More recently it has been grown in tissue cultures by the methods of Rivers and Goodpasture which have almost entirely eliminated bacterial contamination These latter preparations can be used intradermally and produce a much milder reaction with a closed lesion Although the protection afforded against smallpox is probably as solid as that produced by the more usual material sufficient experience with its value in the face of an epidemic of smallpox

has not been obtained as yet to warrant its widespread use

Proper Age for Vaccination —In view of the fact that severe reactions and particularly the complication of encephalomyelitis are less apt to occur when vaccination is performed during the first year, it is best to vaccinate an infant at about the fourth to the sixth month The choice of months however should vary according to a number of factors It is essential that no fixed or invariable order of immunization procedures be followed in infants since epidemics of communicable diseases respiratory infections the convenience of the family and the physician the weather and other factors should all be considered in such procedures It is wise to avoid hot weather because of the possibility of a marked febrile reaction and to avoid vaccination within a certain period following illness and until the latter half of the first year in premature infants or those who have suffered from nutritional difficulties The presence of such cutaneous conditions as eczema impetigo and others should cause postponement of vaccination until the skin is normal but in chronic eczema or in other cutaneous conditions which are not readily curable tissue culture virus injected by the intradermal method can often be used successfully with less danger of bacterial contamination

Choice of Site for Vaccination —It is common practice for girls to be vaccinated on the outer skin of the thigh or on the skin covering the peroneal muscles in the middle of the leg whereas boys are more frequently vaccinated near the insertion of the deltoid muscle on the arm The rubbing of the soiled diaper over the involved area presents certain disadvantages for the thigh area in infants although with sufficient care secondary infection usually can be avoided here also The area of choice therefore is the *outer skin on the middle of the arm or leg* Certain physicians have preferred the inner aspect of the arm in the belief that this area is more fully protected against severe trauma However this variable advantage is more than offset by the greater friction from the clothing and the moderate increase in moisture from perspiration which may occur in this area

Method of Vaccination —In the development of technics for vaccination over many years the objective has been to produce a lesion which results in as inconspicuous a scar as possible and yet which still produces an optimal degree of immunity Although serologic means of determining such immunity are not now available experience in the presence of epidemics of smallpox and with the results of revaccinations has indicated that the take from the recent methods of vaccination resulting in a small scar is as highly protective as the take with the large scar resulting from the older methods of vaccination Unfortunately, many physicians still believe that scarification or drilling of a large area of skin and the resultant disfiguring lesion are essential for a solid and more lasting immunity Even were this true the danger of secondary infections from the larger lesions and the added discomfort and fever would not justify such a procedure

The methods recommended at present are of three types (1) single scratch or incision method (2) drill method (3) multiple pressure method In these methods the objective is to permit the virus to enter the skin in as small an area as possible without sufficient trauma to draw blood The skin of the selected site should be cleansed thoroughly with sterile cotton and ethyl alcohol acetone or ether care being taken to avoid abrasions which might result in multiple takes The site should also be permitted to dry thoroughly after cleansing in order to avoid inactivation of the virus

(1) *Scratch or Incision Method* —A single scratch ⅛ to ¼ inch in length should be made in the skin with a sterile needle or point drawn through the drop of lymph More than one scratch may be made if the first appears to be insufficient but cross scratches should never be used The needle or point should then be placed horizontal with the skin and rubbed gently over the scratched area following which the drop of lymph should be rubbed off lightly with dry sterile cotton

(2) *Drill Method* —Multiple pricks are made through the drop of lymph with the needle held vertical to the skin surface The number of pricks should be limited to five or six and the lymph may then be wiped off with dry sterile cotton

(3) *Multiple Pressure Method*.—The needle or point is held at an angle of approximately 45 degrees with the skin surface and is moved up and down rapidly with pressure on the skin sufficient to puncture it lightly *six to ten times*. *Erythema but no blood or serum should be noted* following the procedure and the lymph may be wiped away immediately with sterile cotton, as in the other methods.

In all of these methods no dressing should be used, but scrubbing the area with soap and water should probably be avoided for *the following twenty four hours*.

Types of Reaction.—In general it may be said that the longer the incubation period the greater is the susceptibility of the vaccinated individual and the more severe is the reaction. The small sized reaction which occurs within the first twenty four or forty eight hours and disappears rather rapidly *denotes a high type of immunity*, whereas the usual "take" with the large reaction, which begins to develop typical signs after five or six days and reaches its height at *eight or nine days is evidence of a highly susceptible individual*. Between these extremes of reaction and susceptibility there are many intermediate responses and *degrees of immunity which follow a characteristic pattern*.

In order of degree of immunity which they indicate, the following reactions can be classified approximately as follows:

(1) *Immune Reaction*.—This occurs as a papule with a light surrounding erythema usually reaching its height within one or two days following the inoculation and then receding quite rapidly in size and reactivity. Individuals showing this type of reaction often have been previously vaccinated within a relatively short time.

(2) *Accelerated Reaction*.—In such individuals the immunity is less than in the preceding case; the reaction reaches its height in from three to five days and there is a vesicle rather than a papule with a marked erythema extending well out from the base of the vesicle. The entire area rarely extends over ½ to ¾ inch in diameter. Slight fever, malaise, chilliness, aching, local tenderness and slight enlargement of the draining lymph gland *frequently occur*. By some this type of reaction has been termed "vaccinoid."

(3) *Primary Vaccination Reaction or Typical Take*.—In the typical "take" little is noted at the site of inoculation except for a punctate area of erythema until the fifth day, when a vesicle appears with a rapidly increasing erythema and induration about it. Usually the vesicle, erythema and induration increase up to the ninth day, when the total area involved ranges approximately from the diameter of a silver half dollar up to the diameter of a grapefruit or even at times beyond in adults. The vesicle itself, if the vaccination is properly performed, rarely exceeds ¼ to ½ inch in diameter, but the area of erythema and induration may not only extend in a wide circular areola but may reach out toward the draining lymph nodes to involve areas of skin many inches from the central vesicle. In certain instances where primary "takes" have occurred by mistake on the tips of the fingers, acute lymphangitis resembling that due to the hemolytic streptococcus may occur during the height of the reaction and extend well up the arm—*apparently the result of the tension produced* in such a restricted area. In the larger reactions, the draining lymph nodes are swollen and tender. Fever is usually present, *in infants at times reaching 104° or 105° F* and remaining at that elevation for several days. Extreme discomfort with chills, aching and localized tenderness is quite common. Also in such reactions small additional vesicles may occur about the periphery of the indurated area. As a result of the irritation and itching, infants will frequently scratch the vesicle and inoculate themselves elsewhere on the body at the site of open skin lesions or scratch marks. As the reaction subsides, the vesicle, which is typically umbilicated, becomes darker in color, with a deeper central crater and gradually changes into a hard black crust which falls off in several weeks. The remaining scar is bluish red at first and in time becomes a firm white area characteristically round and irregularly pocked.

The failure of an individual to react in one of the above manners is not an indication *of immunity, as is often incorrectly supposed*, but is rather an evidence in almost all instances of an inactive virus vaccine. In certain cases the lymph may have been washed

off with soap and water or possibly methyl alcohol or some other improper antiseptic may have been used for preparation of the site of inoculation but it is probable that in only rare instances does the child fail to react when the virus is active and applied properly on a dry site

Care of Reaction —Of primary importance in the care of the lesion resulting from the typical 'take' is maintenance of dryness and a free flow of air about the vesicle For this reason shields should never ing occurs, so that the gauze becomes attached to the vesicle sulfathiazole ointment 5 per cent may be applied to the vesicle at least twice daily following the usual cleansing with alcohol and a piece of gauze may be added as further protection for the clothing

Frequency of Vaccination.—Opinions vary as to the required frequency of revaccination but in general five to seven years may be considered a proper interval between vaccinations with the additional

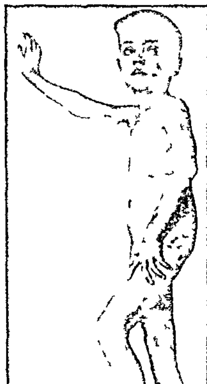
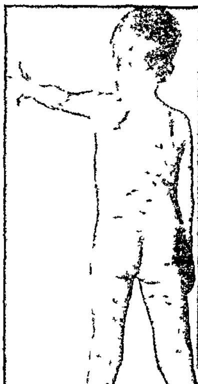



Fig 8—Hyperallergy expressed as roseola vaccinosa Note the marked area of the vaccination lesion on the arm (From the article on vaccinia by Dr Murray Cowie in 5th edition of Cecil s Textbook of Medicine)

be used In addition a relatively sterile surface may be maintained on the vesicle and on the entire area about the reaction by sponging them gently with alcohol and cotton at least twice daily being careful to leave the surface of the vesicle intact If a serous discharge occurs from the vesicle due to excessive tension or as more commonly occurs to trauma alcohol and cotton should be used three to four times daily and a loose piece of gauze attached to the clothing over the vesicle or attached to the skin by adhesive tape placed well outside the indurated area If a discharge sufficient to cause crust

provision that vaccination be performed whenever epidemics of smallpox are pending

Complications and Sequelae —The most dangerous complication of vaccination is that of pyogenic infection This results from neglect dirt scratching and other skin infections Such infection is usually of staphylococcic origin with cellulitis but hemolytic streptococci may at times be responsible and septicemia erysipelas or scarlet fever may also be seen Such infections increase the size and severity of the reaction considerably and result finally in a large and disfiguring scar

The additional necrosis caused by such complications is an excellent medium for the growth of tetanus bacilli Tetanus occurs less frequently now than formerly, but is still an important consideration where dirt and squalor prevail Under such conditions the use of tetanus toxoid for immunization should precede vaccination against smallpox The elimination of shields in the care of the usual take' has also eliminated much of the danger of tetanus

Scratching may cause secondary vesicles at distant points, particularly about the genitalia and face where severe scarring can occur A generalized vaccinia is seen at times in infants with eczema or some other generalized skin disease when it has been exposed to another vaccinated member of the household Umbilicated lesions may extend over most of the body with high fever and extreme toxemia In such cases lesions of the eye should be handled most carefully because of the danger of corneal perforation At times generalized urticaria roseola or purpura are seen when the reaction is at its height

Postvaccinal encephalitis is comparatively rare in the United States but occurs with greater frequency in England and Europe It usually appears about ten days to two weeks following the height of the vaccination reaction although it may be seen earlier or later The severity of this complication appears to be entirely unrelated to the severity of the 'take' The onset is generally abrupt with high fever disorientation and at times with coma or convulsions A stiff neck positive Kernig increase or absence of reflexes and positive Babinski are usually present Weakness and paralysis of the extraocular muscles are common as well as paralyses of the face pharynx, and limbs The white blood cells are increased in the spinal fluid as a rule, chiefly the lymphocytic although at first there may be an increase in polymorphonuclear cells The sugar and chloride of the spinal fluid ordinarily are not greatly altered but the protein is usually increased as is also the spinal fluid pressure The reflex control of the bladder and bowel is often disturbed The course of the disease is usually extremely stormy with either a rapid progression to death or an equally rapid improvement The mortality of this complication ranges from 30 to 40 per cent and even though rapid improvement occurs, residual mental retardation or spasticity may remain There is no specific therapy available other than lumbar punctures for relief of spinal fluid pressure and the proper orthopedic care of any paralyzed or spastic skeletal muscles

JOSEPH STOKES JR

MUMPS

(*Epidemic Parotitis*)

Definition —Mumps is a communicable disease characterized by swelling of the parotid and occasionally other salivary glands, fever and in adults a tendency to complications most frequently orchitis or meningo encephalitis

Etiology —Mumps is caused by a filtrable virus capable of infecting monkeys and possibly cats A parotitis transmissible in series was produced by Johnson and Goodpasture by injecting monkeys directly into Stensen s duct with rather large amounts of saliva collected from patients with mumps When an emulsion of the parotid glands of infected monkeys was sprayed into the throats of susceptible individuals this resulted in the development of mumps and the saliva of one of these patients produced a parotitis when inoculated into monkeys Those immune to mumps were not affected by such spraying Findlay and Clarke confirmed the results of Johnson and Goodpasture

Previously, a number of workers had described a variety of micro-organisms which they believed to be of etiologic significance, but these observations have not been confirmed Martha Wollstein injected filtrates of the salivary secretion of children and adults in the acute stage of the disease into the parotid glands and testicles of cats and produced inflammatory swellings which she considered to be mumps Her results however were less regular than those of Johnson and Goodpasture

Morbid Anatomy —Because of the low fatality there is little information available concerning the pathologic picture in the parotid gland in mumps Johnson and Goodpasture in reviewing the subject described the changes in the infected parotid

gland as consisting of an interstitial serous exudate, an interstitial fibrinous exudate catarrhal inflammation of the excretory ducts foci of hemorrhage an interstitial infiltration by leukocytes desquamation of the epithelial cells with a leukocytic infiltration of the tubules and edema of the glandular epithelium, an intense, interacinar vascular congestion marked periglandular edema and changes of early necrosis in the glandular epithelium'

In the experimental mumps of monkeys the changes were quite similar and cytoplasmic inclusions were described in the acinar cells Bloch observed that the cytoplasmic inclusions occurred in the absence of the mumps virus and therefore he did not consider them specific for the disease

Symptoms —*Incubation Period* —As a rule the incubation period is from seventeen to twenty-one days after exposure although some authors quote figures of fourteen to twenty five days Incubation periods of less than one week or as long as four weeks have been reported but these are quite unusual

Communicability —Close contact is usually necessary for the transmission of mumps and a relatively small proportion of children exposed contract the disease as compared with the incidence of infection in measles or chickenpox The virus is present in the saliva and is disseminated by droplet infection or mechanically as for example by contaminated hands The portal of entry of the virus is probably the mouth

Mumps affects persons of all ages but is most frequent between the ages of five and fifteen years The disease is infrequent in children under two years of age and infants are usually immune up to the eighth or tenth month However cases of mumps in both infants and newborn have been reported

The disease occurs in all parts of the world most commonly in epidemic form The climatic conditions seem to have little effect on the prevalence of mumps but the greater number of cases tend to occur in the winter and spring

The period of contagion of mumps is unknown but it is presumed to last from the beginning of symptoms until the disappearance of the swelling of the glands involved A few cases have been cited of infection by contact before symptoms were observed but this is extremely rare The usual custom is to isolate all cases for three weeks after the onset of symptoms Contacts are commonly quarantined for twenty-one days after exposure

Immunity —One attack ordinarily confers immunity for life Second and third attacks have been observed but these observations have been questioned by some Macleod in an analysis of 694 cases of mumps in adult males noted that seventeen stated that they had had mumps previously and one said that this was his third attack

Mode of Onset —The severity of mumps varies greatly and in mild attacks the first symptom is usually pain below the ear, followed rapidly by swelling of the parotid gland and a rise of temperature to about 101° F In severe cases there may be a prodromal period of twenty four to forty-eight hours characterized by fever malaise chilliness anorexia and headache and after the appearance of parotitis the temperature may rise as high as 103° to 104° F The enlargement of the parotid gland usually progresses reaching its maximum on the second day The enlarged gland is as a rule firm and somewhat elastic frequently both glands are involved although the second may not be affected for several days after the first The swelling is generally below and in front of the ear and may extend back to the sternomastoid muscle the lobe of the ear being somewhat elevated and in the center of the swollen area The submaxillary and sublingual glands may at times be involved and in rare cases may be affected without the parotid gland

Clinical Course —The temperature and swelling generally reach their maximum on the second day after which they gradually return to normal The average duration of symptoms is seven days in uncomplicated cases The disease may however last much longer and swelling has been known to persist for a number of weeks Relapses after twelve to fifteen days have been described as occurring in about 10 per cent of the cases

Complications —*Orchitis* is extremely rare before the age of puberty probably not more than 1 per cent In epidemics among adults the incidence is much higher varying

in different reports from 10 to 50 per cent and averaging about 18 per cent

The onset is usually between the fifth and tenth day after the parotid swelling, and is characterized by a rise in temperature pain and swelling in the affected testicle, and frequently by general malaise, chilliness discomfort in the inguinal region and occasionally nausea The swelling progresses for two or three days and then gradually subsides returning to normal in seven to ten days Occasionally the course may be much longer and more severe The inflammation is in the testicle usually and not in the epididymis Only one testicle is involved as a rule but both may be affected Rarely orchitis may be the only manifestation of mumps

Atrophy of the testicle as manifested by a reduced size of the gland, is rather frequent apparently taking place in 40 to 60 per cent of the cases Impotence and sterility, although they do occur are not common

Meningo encephalitis is not of uncommon occurrence although its frequency is difficult to determine An incidence as high as 23 per cent has been reported in some epidemics All ages are affected and there is no evidence that sex plays a part

The symptoms of meningo encephalitis begin toward the end of the first week of illness There is a sudden rise of temperature, headache stiffness of the neck and a positive Kernig s sign are the most frequent manifestations Delirium may occur but is not the rule The spinal fluid is under increased pressure is clear or slightly opalescent and shows a pleocytosis composed largely of mononuclear cells which may at times be as high as 1200 although this is exceptional

The prognosis is good Deaths have been reported but they occur only rarely In sixty cases observed in the meningitis division of the Bureau of Laboratories, New York City Department of Health no deaths occurred

The severity may vary greatly Finkelstein reported six cases who had only a slight rise of temperature for twelve to twenty four hours and no clinical signs of meningo encephalitis but who nevertheless showed a pleocytosis on lumbar puncture This would tend to show that involvement of the central nervous system is more frequent than is commonly recognized

Deafness is of occasional occurrence and may be permanent This is assumed to result from inflammatory involvement of the labyrinth

Pancreatitis, nephritis mastitis and involvement of the lacrimal glands are occasional complications

Suppuration of the parotid gland has been reported in less than 1 per cent of the cases and is attributable to secondary infection

Diagnosis —During epidemics diagnosis is simple the long incubation period characteristic parotid swelling, and clinical course being sufficient It is only during epidemics that cases in which only the submaxillary glands are involved can be diagnosed

The blood picture may at times be of assistance There is an increase in white blood cells with an absolute and relative lymphocytosis The pulse is frequently slow and may be 50 to 60 per minute

Differentiation must be made between parotitis caused by bacterial infection which is usually secondary to some other diseases cervical adenitis secondary to septic sore throat diphtheria or scarlet fever, tuberculous adenitis Hodgkin s disease This is usually not difficult

Prognosis —The prognosis is good, and fatal terminations are extremely rare—less than 1 per 1000 Complications are uncommon in childhood and are more frequent after the age of puberty

Treatment —Rest in bed is desirable so long as fever or swelling persists The mouth should be kept scrupulously clean in order that secondary infection of the parotid gland may not occur Ample fluids and a soft diet should be given while fever is present Mild sedation may be necessary

Orchitis is treated by support of the testicles Local applications may alleviate discomfort It is said to occur more frequently in patients who have not been confined to bed

Meningo encephalitis is treated symptomatically Lumbar puncture usually relieves headache, but sedatives may also be required

Prophylaxis—Isolation for three weeks is customary Convalescent serum injected in a dose of 2 to 8 cc has been used for passive protection within six days after exposure The results are suggestive but the available information is not adequate for proof of the effectiveness of this procedure

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PSITTACOSIS

Definition—Psittacosis is a specific infectious disease of parrots parrakeets love birds and other members of the parrot family The malady is highly communicable to man

History—Ritter 1880 first adequately described psittacosis as a disease entity in man designated it "pneumotyphus and associated it with the presence of sick birds in the patient s home Nocard 1892 discovered *Bacillus psittacosis* which subsequently was shown to be identical with *B aertrycke* and not the cause of psittacosis Bedson and others 1930 showed that the etiologic agent of psittacosis is filtrable Levinthal 1930 found minute coccoid bodies of diagnostic importance in infectious material Krumwiede 1930 showed that white mice are susceptible Rivers and Berry 1930 1932 experimentally induced psittacosis pneumonia in monkeys and devised a method using white mice instead of birds whereby one may test for the presence of psittacosis virus in a patient s sputum

Epidemiology—Man usually contracts the disease from members of the parrot family canaries or finches Recently it has been shown that fulmars chickens and pigeons are subject to natural infection with psittacosis virus These birds when infected can pass the disease to human beings but are less dangerous in this respect than are members of the parrot family A carrier state probably exists in birds Psittacosis never pandemic in nature manifests itself in a given population by isolated household epidemics Transmission of the disease from man to man occurs, but not frequently Both sexes and all ages are susceptible Children however appear to be more resistant than adults The virus found in the nasal discharges and droppings of infected birds and in the sputum of patients is stable withstanding prolonged drying and enters man through the mucous membranes of the upper respiratory tract

Etiology—The inciting agent is filtrable and has not been shown capable of multiplication on ordinary media The minute coccoid bodies described by Levinthal and subsequently shown by Bedson to be specifically agglutinated by immune serum are considered by many investigators to represent the virus

Morbid Anatomy—In the parrot and the mouse the lungs are rarely involved The liver is enlarged and studded with areas of necrosis The spleen the normal architecture of which is destroyed is enlarged and contains areas of focal necrosis In man and the monkey the striking feature of the disease appears in the lungs and is characterized by a patchy consolidation starting near the hilum and spreading toward the periphery of the organ Only slight if any involvement of the pleura is seen Bronchitis is not a pronounced feature In stained sections the alveolar walls show a marked cellular infiltration and the alveolar spaces are filled with mononuclear cells and fibrin. In fact the cellular infiltration or proliferation of cells in the alveolar walls including an active proliferation of the alveolar epithelium giving rise to rows of cuboidal cells lining the alveolar spaces is characteristic of psittacotic infections of the lungs Congestion and thrombosis of capillaries occur and often the alveolar walls become necrotic If the lungs are secondarily invaded by pneumococci or streptococci the pathologic picture is altered accordingly The liver may show fatty degeneration with areas of focal necrosis The spleen may or may not be enlarged and at times shows hyaline de

generation of the smaller vessels No specific changes have been found in the brain

Incubation—The incubation period in the majority of instances is eight to fourteen days

Symptoms—The onset of the disease is usually abrupt with malaise anorexia headache, backache photophobia and chills Headache, restlessness, insomnia, delirium, typhoidal state, nonproductive cough, constipation with abdominal distention and tenderness, are as a rule present during the height of the infection A few cases exhibit a diarrhea Epistaxis occurs in about 25 per cent of the cases In a number of instances rose spots have been seen The temperature rises rapidly and after a period of continued elevation begins to fall by lysis during the second or third week The pulse is relatively slow Pleural pain is usually absent and the respiratory rate is only slightly increased A decided increase in the pulse and respiratory rate indicates a bad prognosis Only rarely does consolidation of the lungs fail to make its appearance It starts at the hilum and spreads toward the periphery Physical signs may appear slowly but x ray examinations indicate that the lung involvement comes early in the course of the infection The x ray picture is not unlike that seen in influenzal pneumonia As a rule the cough is nonproductive Sputum when produced is usually tenacious but not rusty A few patients however bring up large amounts of sputum over long periods of time White blood counts reveal a slight leukocytosis at the onset of the infection with a tendency toward a leukopenia later Relapses occur Phlebitis is not an infrequent complication Convalescence is slow and tedious

Diagnosis—An atypical pneumonia accompanied by slow respiratory and pulse rates, a normal or low white blood count an absence of pleural pain an intense and persistent headache and a typhoidal state in an individual associated with birds, particularly members of the parrot family should suggest the possibility of psittacosis The disease is most likely to be confused with typhoid fever influenza or atypical pneumonias not caused by the virus of psittacosis Typhoid fever is excluded by negative blood and stool cultures and a negative Widal reaction Results of the mouse test for the presence of psittacosis virus in the sputum indicate whether or not one is dealing with a psittacosis pneumonia The complement fixation reaction is a diagnostic aid

Prognosis—The mortality rate, given as 35 to 40 per cent, is probably too high inasmuch as a number of mild cases may have been overlooked Individuals under thirty years of age are less likely to die than are older ones

Prophylaxis—Avoid birds likely to be infected The virus is in the sputum and this fact should be borne in mind by those caring for psittacosis patients

Treatment—The treatment is symptomatic

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LYMPHOGRANULOMA INGUINALE

(*Climatic Bubo Nicholas Favre Disease Lymphopathia Venereum*)

Definition—Lymphogranuloma inguinale is a specific infectious venereal disease characterized by a transient primary lesion often

overlooked followed by a subacute lymphadenitis with suppuration fistulae and eventual cicatricial healing

Incidence—Formerly thought to be largely a disease of the tropics particularly affecting males it is now known to be endemically prevalent in temperate as well as tropical zones and to occur in both sexes though in somewhat different clinical forms

Epidemiology—The usual method of infection is by sexual intercourse but the infection may be contracted by nonvenereal contact and has occurred following accidental inoculation

Etiology—Lymphogranuloma inguinale is caused by a filtrable virus which can be isolated from the lesions and transmitted experimentally to monkeys guinea pigs and mice (Hellerström and Wassen) Elementary bodies similar to those of vaccinia are found in pus from the lesions (Coles)

Pathology—The pathology varies with the intensity and duration of the infection In general it consists of an inguinal and pelvic lymphadenitis Multiple abscesses develop in the affected lymph nodes and discharge through fistulous openings Subsequently scar tissue formation ensues and may lead to rectal stricture and elephantiasis of the external genitalia Histologically the lymph nodes and surrounding tissues present the picture of a subacute or chronic infectious granuloma

Symptoms—The incubation period from the time of exposure to the onset of adenitis is ten to fifty days Some time during this period an evanescent primary lesion on the prepuce or glans may be noted in males In females primary lesions of the external genitalia are rare being commoner on the vaginal wall or cervix The adenitis usually first involving the inguinal lymph nodes in men and the pelvic nodes in women begins insidiously and runs an indolent course The onset may be accompanied by mild systemic symptoms of malaise headache anorexia and moderate fever With the development of periadenitis the overlying skin becomes attached and dark red or purplish Areas of softening appear in the nodes and eventually discharge a seropurulent fluid through fistulae which may drain for weeks or months Arthritis is reported to occur in many cases In women with pelvic and perirectal adenitis the condition may pass unrecognized or anal fistulae with purulent discharge from the rectum and painful defecation may herald the onset Since these symptoms may simulate those of ulcerative colitis a Frei test is desirable in patients with this disease Late sequelae due to contractile cicatricial healing are rectal strictures and elephantiasis of the scrotum and penis in males or of the vulva and perianal region in females Indolent ulcerative lesions about the genitalia in women a condition known as esthiomene may complicate the picture

Diagnosis—The diagnosis depends primarily upon the history and clinical picture It has been greatly facilitated by the intra



Fig 9—Lymphogranuloma inguinale Unilateral involvement 5 days after appearance of inguinal adenitis (Courtesy of Howard and Strauss New England Journal of Medicine)

dermal test described by Frei which should be used in all suspected cases In general the Frei test for cutaneous sensitivity is specific and becomes positive by the time periadenitis has developed Since it apparently remains permanently positive it must be kept in mind that a positive test does not necessarily permit a positive diagnosis of the lesion under consideration but may be only an indication of a previous infection Hyperglobulinemia accompanies the active stages of the infection

Treatment—No specific cure is at present available The treatment of choice would appear to be surgical extirpation of the affected nodes prior to suppuration and fistula formation combined with rest and medical

supportive measures Chemotherapy with the sulfonamide derivatives is reported to be helpful in some cases

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FOOT AND MOUTH DISEASE

(*Aphthous Fever Epizootic Aphthae Epizootic Stomatitis*)

Definition —Foot and mouth disease is a contagious malady of cloven footed animals *e g* cattle pigs sheep and goats Guinea pigs and hedgehogs are susceptible to experimental infection Upon rare occasions man becomes infected and the disease in the human host is characterized by a febrile reaction and a vesicular eruption in the mucous membrane of the mouth which at times also involves the skin of the hands and feet

Incidence —In many parts of the world the disease is enzootic and often becomes epizootic Lower animals in the United States are relatively free from the malady, consequently, human beings in this country are not frequently exposed to it In fact man is not highly susceptible as is evidenced by the fact that nine volunteers failed to develop signs of the disease following inoculation of the virus into their soles and palms Nevertheless it has been definitely shown by means of inoculation of vesicular material from patients into guinea pigs that at least five human beings have had foot and mouth disease Man usually contracts the disease from infected low animals or from the products of such animals, transmission from man to man is unknown

Etiology —Loeffler and Frosch showed that the etiologic agent is a filtrable virus Their findings have been abundantly confirmed and now it is known that the virus is exceedingly small possessing a diameter of 8 to 12 millimicrons The causative agent is found in the milk butter saliva urine feces, hides and meat from infected cattle

Symptoms —After an incubation period of two to fourteen days the patient develops fever and vesicular lesions in the mucous membrane *of the mouth and on the lips* Similar lesions may appear on the soles palms *and the interdigital skin of the fingers* and toes Within a few days the fever sub*sides and the lesions heal without the formation* of scars

Diagnosis —*All vesicular lesions in and* around the mouth are not caused by the *virus of foot and mouth disease A correct* diagnosis can be arrived at only by means of *tests properly conducted in a susceptible* host *e g* the guinea pig One should remember *however that in the United States per*mission to make such tests must be obtained *from the Bureau of Animal Industry in* Washington

Prognosis —*In man the disease is mild* and complete recovery is the rule

Prophylaxis and Treatment —*In countries where the disease is enzootic or epizootic pasteurized milk or milk products* should be used Treatment is symptomatic

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LYMPHOCYTIC CHORIOMENINGITIS

Definition—Lymphocytic choriomeningitis is an acute disease of man characterized by a lymphocytic reaction in the meninges monkeys and mice are also susceptible to natural infection guinea pigs are susceptible to experimental infection

Incidence—The disease has been definitely recognized for only a short time but within that period the virus causing it has been recovered from a number of patients in America and abroad

Etiology—A medium sized virus has been shown to cause the malady It has been isolated from the spinal fluid and blood of patients during the acute stage of the disease and antibodies against the virus which develop relatively slowly have been demonstrated in the blood of recovered patients Spinal fluid and blood (1–2 cc) from patients suspected of having the disease should be injected subcutaneously into guinea pigs If virus is present the pigs will develop a fever within seven to nine days and will usually die within twelve to eighteen days Passages from pig to pig can be made by means of blood or an emulsion of the brain

Symptoms—A period of generalized pains and malaise followed by severe persistent headache nausea and vomiting nuchal rigidity Kernig s sign and fever accompanied by a relatively slow pulse are the symptoms and signs usually encountered The white blood cell count is not particularly abnormal Lumbar punctures reveal spinal fluids under increased pressure containing a normal amount of sugar an increased amount of protein and an increased number of cells (200–1700 per cubic millimeter) which are predominantly lymphocytes The fever usually disappears within a week at which time the patient begins to feel much better but the cell count in the spinal fluid may return to the normal level much more slowly

Pathology—The pathologic picture in human beings is as yet not well defined The virus however produces a lymphocytic choriomeningitis and an interstitial pneumonia in monkeys mice and guinea pigs

Diagnosis—In 1925 Wallgren described what he considered a clinical entity and designated it acute aseptic meningitis' There are reasons however to believe that all cases that conform to Wallgren s criteria for acute aseptic meningitis' are not caused by one kind of virus Some undoubtedly are induced by the virus of lymphocytic choriomeningitis and should be removed from the group of cases known as acute aseptic meningitis and placed in a separate category designated as lymphocytic choriomeningitis Neutralization and complement fixation tests are diagnostic aids

Prognosis—Individuals afflicted with this disease rarely if ever die complete recovery is the rule but an occasional patient experiences sequelae

Treatment—Repeated lumbar punctures and intravenous injections of hypertonic solutions of glucose seem to relieve the headache which is a very prominent symptom of the malady

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HYDROPHOBIA

(*Lyssa Rabies*)

Definition—Hydrophobia is an acute infectious virus disease usually transmitted in the saliva of a rabid animal It is characterized by a variable incubation period by symptoms of irritability of centers in the brain and by psychic excitation and hyperesthesia followed by paralysis and death

History—Rabies was described by Aristotle Celsus and Galen In 1804 Zinke demonstrated its infectious nature by successfully inoculating animals with the saliva of rabid dogs

In 1881 Pasteur proved that the virus is always present in the central nervous system and can be transmitted by subdural inoculation with the brain of a rabid animal In 1884 he showed that animals can be protected by the subcutaneous injection of spinal cord containing the virus which has been modified by passage through a series of rabbits and attenuated by drying

Incidence—The disease occurs in all countries and climates and at all seasons of the year All mammals and most warm blooded animals are susceptible, but responsibility for its presence rests on the dog

Etiology—The virus is filtrable, and is altered and destroyed by chemicals and by physical agents as heat drying and sunlight

It enters through a bite, or when the saliva comes in contact with an open wound or with the mucosa of the lips or nose The virus travels in the nerves to the brain multiplies there and passes out along the efferent nerves of the salivary glands into the saliva

Morbid Anatomy—At autopsy the only gross change found is a marked congestion of the vessels in the meninges and the brain In most cases a microscopic examination of the cornu ammonis shows the presence of characteristic inclusion bodies described by Negri A positive diagnosis of rabies is made whenever these are present Unfortunately it is *not* always possible to demonstrate these structures hence the failure to find them does not exclude the possibility of rabies

Throughout the brain there may be found a perivascular infiltration of small round cells and in the gasserian and sympathetic ganglia there is usually an infiltration of endothelial cells with destruction of the nerve cells However these changes are found in other diseases

Incubation—The incubation period varies from ten days to two or more years The average is fifty to sixty days In dogs it is usually between fifteen and thirty days but may be as long as a year or more

The length of this period is influenced by the location and extent of the bite and by the species of the biting animal Since the virus travels along the nerves it reaches the brain more quickly and symptoms develop earlier when the bites are on the face and head than when the injuries are on the hands, likewise these latter have a shorter period than bites on the feet and legs

Bites of wolves and other wild animals are more dangerous than those of dogs partly because these animals, being ferocious, bite more deeply, and partly because passage of the virus through such carnivora increases its infectivity

In this country rabies in man is usually due to the bite of a dog Cats wolves skunks and other animals make up less than 10 per cent of infective agents It is estimated that 10 to 15 per cent of all persons bitten will develop hydrophobia unless immunized The mortality from bites on the face and head will average 60 to 70 per cent, those on the hands 15 to 20 per cent those through clothing 1 per cent The more extensive the injury the greater the mortality Contact in the absence of a wound is rarely followed by rabies Alcoholism exposure to extremes of heat and cold fatigue and fear are factors in the development of the disease

Symptoms—In *dogs* there are two types of the disease furious and dumb, but these two forms may merge or appear at different stages in the same animal

In the *furious* type one of the first symptoms is an altered disposition The gentle dog becomes morose does not bark joyously seeks seclusion hides and refuses food Frequently it becomes more friendly than ever refuses to leave its master s side tries to lick his hand and face and redoubles its affection Twelve to forty eight hours later it grows unnaturally restless comes and goes incessantly rests for a moment lying down then jumps up brusquely moves to another place in evident agitation and again resumes its restless movements It may make no effort to bite and may obey all commands, but is unable to remain quiet and acts as though under a strange and unnatural compulsion Short periods of repose are followed by increased agitation Irritation over any restraint is marked Strangers are attacked without warning

As the disease progresses it snarls viciously barks and growls menacingly at imaginary objects turns suddenly as if to defend itself It chases and bites animals around the house and farm the cats dogs poultry horses cows and other domestic animals with which it had previously lived

peacefully The animal if housed is agitated and excited scratching tearing and upturning its bedding gnawing at furniture and grabbing viciously at any object pointed at it If free, it leaves the house and travels long distances biting such animals as it may encounter though not going out of its way to seek a quarrel and not remaining near its victims It attacks and passes on At last haggard emaciated it falls from the oncoming paralysis or unsteadily makes its way back to its home to die

The so-called dumb or paralytic type is very common (20 per cent), but is usually unrecognized except by veterinarians The stage of excitement and irritability is absent or unnoticed The attack is more fulminating the progress more rapid From the beginning the animal is evidently ill and anxious but not excitable

Paralysis may begin in any muscle or group though usually the first noted is in the lower jaw It cannot close its mouth the tongue protrudes saliva flows in excess Paralysis rapidly extends to other parts of the body and death follows in two or three days It is this condition which leads sympathetic people to imagine the dog has a bone in its throat and to try to remove it In doing so their hands become covered with saliva

The disease occurs in dogs at all times of the year but more persons are bitten in the summer because at this season more men women and children are on the streets or out of doors

In man the disease is frequently ushered in with a short prodromal period of mental depression a feeling of impending danger insomnia Ungovernable restlessness seizes the patient Melancholia is common Hyperesthesias of the skin to changes of temperature and especially to currents of air and increased sensitiveness to sound and light mark the progress of cerebral irritation A patient weighed down with terror often becomes maniacal the restlessness increases to uncontrollable agitation An excessive flow of thick tenacious saliva pours over the face and neck and becomes smeared on his hands and clothes and over the bedding and floor Periods of rage are followed by moments of calm in which the patient usually shows anxiety for the safety of those around him and warns them of the approach of another crisis Convulsions are brought on by the least irritation and by the slightest current of air Aerophobia is one of the most characteristic symptoms of rabies Blowing the breath on the neck of a patient often precipitates convulsions and is valuable in differentiating this disease from hysteria The slightest breeze brings on respiratory difficulties the breath comes in spasms dyspnea is extreme and there are epileptiform seizures or tetanic rigidity

The symptom which gives to the disease its common name *hydrophobia* appears as a rule twenty four to forty eight hours after the onset It is rarely absent This symptom due to the reflex irritability of the center of deglutition gives rise to those laryngeal spasms so agonizing to the patient and so distressing to the attendants as to justify the universal dread of the disease When the victim lifts the glass to his lips there is an immediate viselike contraction of the muscles of deglutition with an excruciatingly painful spasm of the glottis and pharynx The body trembles with convulsive movements the jaws are clenched respiration is impossible The patient feels that he is being strangled to death and may die suddenly during the spasm After several attempts to drink the pain is so terrible that despite the intense thirst he cannot be induced to try to swallow liquids and the sight of water or mention of the word brings on an attack Death occurs as a rule after two or three days from cardiac or respiratory failure

A paralytic form occurs in man in which symptoms of cerebral irritation are wanting After an onset with high fever neuralgic pains in the region of the bite are followed by weakness and paresis of the muscles of this part Paralysis becomes general and death occurs in from three to five days

Diagnosis —In man the diagnosis is rarely difficult The history of exposure the length of the incubation period and the clinical symptoms serve to differentiate it from tetanus Fear of the disease may result in a hysterical state closely simulating the real disease These persons are relieved by suggestion or proof that they have not been exposed Hysteria is rarely fatal A microscopic examination of the brain and the in

oculation of animals will establish the diag nosis in doubtful cases

Prognosis—Once the symptoms have developed, death is inevitable The pain and excitement are controlled by large doses of sedatives chloral morphine coal tar preparations, chloroform or other anesthetics

Treatment—This is the destruction of the virus at the time of injury and preventive immunization

Local—The wound should be mechanically cleansed and cauterized with pure carbolic acid followed immediately with 95 per cent alcohol Nitric acid is advocated, but its use is more painful and probably no more effective Cauterization cannot be relied upon to destroy all the virus but its use has been shown to result in a prolonged incubation period The next and most important step is to determine whether or not the biting animal is rabid It should never be killed unless to protect others until the diagnosis can be confirmed or excluded by observation while alive It is not always possible to find microscopic evidence of rabies in the brain especially if the animal is killed *early in the disease The saliva of a dog may* be infectious from four to six days before the appearance of symptoms if therefore the animal appears normal and remains so for a period of ten to fourteen days the possibility of infection may be dismissed

Any biting animal should be suspected of being rabid until proved otherwise An animal that cannot be confined and observed should be regarded as rabid

General—In all cases where the animal is known to be rabid or when it cannot be examined the patient should receive Pasteur treatment as promptly as possible The value of the Pasteur treatment for rabies has been widely accepted but recently some doubt as to its efficacy has been raised by Webster who bases his misgivings on both experimental and statistical grounds While there may be some scientific basis for this skepticism the majority of immunologists still retain their faith in the Pasteur treatment and a practitioner would not be justified at the present time in advising his patient against its use

The mortality of those promptly treated is less than 1 per 1000 Deep or lacerating wounds on the head or hands require the so called intensive treatment' in which larger amounts of vaccine are given

No preparation of the vaccine is invariably effective or entirely free from dangerous sequelae In very rare cases the injection of the vaccine is followed by severe and sometimes fatal paralysis This appears to be due to an individual sensitiveness to rabbits brain and cord and is not the result of an infection by the vaccine

Because of this danger rabies vaccine should not be given if it is evident that the offending animal is not rabid and if it continues to act normally while under observation

Suppressive Measures—The destruction of all ownerless dogs and the temporary muzzling or restraint of the rest by their owners is the one and only method of eradicating this disease This has proved successful in England and in the Scandinavian countries where the disease once as common as it is here has completely disappeared

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POLIOMYELITIS

(*Infantile Paralysis*)

Definition—A common acute virus disease which may give rise to myelitis often resulting in flaccid paralysis of various groups of muscles It is prone to appear in epidemic form particularly in the summer time and children are more susceptible than are adults It is characterized by sudden onset with a brief period of fever and malaise which is the extent of the clinical picture in many of the cases

History—Reference to conditions which may have been poliomyelitis dates from earliest times but no descriptions of this disease have been found in medical literature prior to the end of the 18th century At this

time mention of acute paralysis in childhood was made in England by Michael Underwood in his textbook on diseases of children During the subsequent fifty years there are several descriptions of poliomyelitis the best being that by the German orthopedist Heine (published in 1840) who was apparently the first to understand the nature of this disease Strangely enough the epidemic character of poliomyelitis did not receive emphasis until Medin's work appeared in Sweden in 1890 From that time forward the disease ceased to be a curiosity and became in some countries a periodic scourge The principles of its epidemiology were first reviewed by Medin's pupil Wickman who published his monograph in 1908 the same year in which Landsteiner discovered the virus Three years later Kling and his associates in Stockholm laid the foundation for the more modern types of clinical investigation in poliomyelitis They were also responsible for pointing out the intestinal phases of this disease

Etiology —The virus of poliomyelitis has sufficiently distinct properties to permit its identification with considerable accuracy Its size estimated at approximately 10 to 15 millimicra marks it as one of the smallest filtrable viruses In comparison with many bacteria it is quite stable remaining viable at ice-box temperature in aqueous suspensions of feces for months and similarly in pieces of infected spinal cord stored in 50 per cent glycerine for years It can also survive in weak solutions of phenol and in high concentrations of ether, but is readily destroyed by oxidizing agents such as hydrogen peroxide potassium permanganate by ultraviolet rays and by heating for a short period of time to a temperature of 55° C Its resistance to chlorine has not been accurately determined but probably the amount of chlorination adequate for killing enteric bacteria in water may not suffice to destroy the virus of poliomyelitis

Another characteristic of this virus is its narrow host range for it is pathogenic only for certain monkeys and chimpanzees although perhaps in some instances for certain rodents—notably the eastern cotton rat As with other neurotropic viruses a number of different strains have been described An appreciation of this multiplicity of strains is important when one comes to an estimate by neutralization tests of immunity to this disease—both in animals and in man As a rule such tests are not very practical nor has it yet been possible to demonstrate specific immunologic reactions by means of precipitin tests complement fixation tests or cutaneous tests such as are used with many other infectious diseases This has seriously limited the study of human immunity to poliomyelitis

Epidemiology —Children are more susceptible than adults and in this respect poliomyelitis resembles such common diseases as diphtheria or measles But unlike diphtheria and measles poliomyelitis does not seem to be a respiratory disease How the virus of poliomyelitis enters the human body is still a matter of conjecture but it is unlikely that it gains access to the central nervous system solely by way of the olfactory bulbs It may penetrate through a number of possible portals including the mucosa of the oral cavity the lower gastrointestinal tract, or conceivably the skin Once in the body the virus shows affinity for two areas in particular (1) the intestinal tract (viz the lower ileum), where it may survive with or without the production of myelitis and (2) certain areas of the central nervous system

Regardless as to how the virus enters the body one of its major portals of exit is through the gastro intestinal tract A convalescent patient may harbor the virus here for months but usually it is demonstrable in the feces only for about three weeks after an acute attack *Healthy carriers* have also been described and Francis and his co workers have presented circumstantial evidence that healthy children may carry the virus for a month or more prior to their acquisition of the disease As a rule these carriers (both convalescent and healthy) are children under the age of six years The part which they may play in the general spread of the disease is unknown Dissemination of the virus might therefore result from direct human contact (which is the most commonly accepted view) or from contaminated objects including food An extra human reservoir of the virus in the form of infected insects (notably flies) mammals or birds is also a distinct possibility although the virus has been demonstrated in nature only in the first of these two groups

Summer weather and environmental factors are important influences in that epidemics are more apt to occur in the summer and early fall than at other times of the year and they are particularly prone to flourish in suburban or rural surroundings They are uncommon in institutions or in

oculation of animals will establish the diagnosis in doubtful cases

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History—Reference to conditions which may have been poliomyelitis dates from earliest times but no descriptions of this disease have been found in medical literature prior to the end of the 18th century At this

not been given) Fever is almost universal it is generally over 100° F lasting from one to four days Occasionally there is pain in the back, and occasionally a stiff neck but in general the physical signs are indefinite

In a typical *paralytic case* the onset and the clinical picture for the first two or three days are similar but the disease usually lasts longer with fever of from three to ten days —although generally not more than six In almost half of the cases there may be two bouts of fever, with myelitic symptoms confined to the second bout Early evidence of central nervous system involvement is indicated by stiff neck as a cardinal symptom and with it there may be fretfulness or restlessness apprehension yawning drowsiness and even stupor Pain in the limbs twitching and sensitivity to touch and pressure should be carefully noted as they may be the forerunners of paralysis The later days of fever mark the period in which signs of meningitis and myelitis may become more pronounced and in which flaccid paralysis may appear with considerable rapidity Muscle weaknesses may vary from quick fatigability to complete paralysis During this period of active myelitis retention of urine and constipation are not uncommon particularly when severe paralysis of the lower extremities and abdomen is present

Different clinical pictures arise depending on the region of involvement in the spinal cord and brain Thus we are accustomed to speak of *bulbar poliomyelitis* and the *encephalitic form of poliomyelitis* as well as *paralytic poliomyelitis* But it is seldom that the disease picture is limited solely to one of these various types With the bulbar type which occurs when the medullary centers are involved and is one of the most serious forms of the disease the first indications may be a report by the parents that the child s voice has a nasal tone or that there is difficulty in swallowing sometimes resulting in fluid being extruded from the nose With progression the inability to swallow becomes more serious and mucus and saliva accumulate in the throat Attempts to drink water cause coughing and gasping As the disease progresses the patient often becomes disoriented and comatose Attempts to examine the throat lead to choking and resistance

Diagnosis —There is no diagnostic test which can be efficiently applied in the early stages of poliomyelitis for the initial symptoms are apt to be nonspecific in character but headache, stiffness of the neck and/or the back are the most important symptoms Almost as important as the symptoms, are the circumstances under which they are found viz one should be concerned about poliomyelitis when the above symptoms occur during the summer or early fall or during epidemic times Under these circumstances a cardinal sign is fever that is fever higher than 101° F which is otherwise unexplained When poliomyelitis is suspected the neck and spine should be carefully examined viz place the child in a sitting position on the floor with the knees spread apart and press the head down between the knees Kernig s sign may be uninformative

Vigilance (not to be carried to the extent of daily exhaustive complete muscle tests) should be used for the early detection of weakness in muscles groups of muscles or limbs The reflexes may be erratic and normal reflexes may be found even while a patient is developing or has developed paralysis At first however the reflexes may be hyperactive becoming diminished or absent with surprising rapidity as weakness develops The physical examination should also include a search for ocular palsy facial palsy changes in the character of the voice paralysis of the soft palate and changes in the state of the respiratory and abdominal muscles

The *lumbar puncture* may be of considerable diagnostic aid but the findings are not pathognomonic In all cases in which there are well marked clinical signs of meningitic involvement and this includes both paralytic and nonparalytic cases the cell count is apt to be increased ranging from 15 to 150 cells or even many more They are largely mononuclear cells (50 per cent to 95 per cent) but cases with 80 per cent polynuclears in the spinal fluid may occur In a greater per cent of cases there is an increase in globulin However in the majority of abortive cases and occasionally even in the paralytic case the spinal fluid may be normal

In the acute and early stages the blood

homes for children, but are not infrequently seen as small outbreaks in summer camps In nature the virus has been isolated from sputum from human feces, from a privy, from sewage and from flies, and it may be far more widespread than these sites indicate

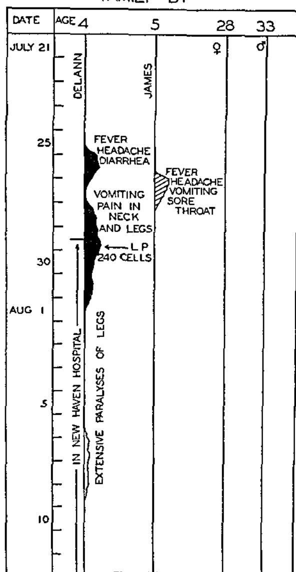


Fig 10—Diagram of a family with poliomyelitis Vertical lines indicate the family members their ages appear at the top Both children became ill at about the same time eventually one became paralyzed The presence of paralysis aids in the clinical diagnosis but it does not aid in determining which of the two children will excrete the most virus in their stools

Recent tonsillectomy operations (within six months) tend to lower the resistance of children and render them more susceptible than normals to the more serious forms of the disease Contrary to earlier teachings multiple cases within families are common although usually not more than one case in a family becomes paralyzed at a given time (Fig 10) There is evidence to suggest however, that in certain families a high prevalence of the paralytic form of the disease has prevailed through several generations

Morbid Anatomy—Important lesions occur in the gray matter of the spinal cord but it is a mistake to think of this disease as existing wholly in that part of the body Classical lesions, which are associated with paralysis, are the result of the neuronotropic *tendencies of the virus They involve the* ganglion cells in the anterior horn of the spinal cord particularly in the cervical and lumbar regions These lesions pass through several stages but at their height and later, they are characterized by destruction of neurons neuronophagia and perivascular and interstitial round cell infiltration In the brain the lesions show a selectivity for the motor cortex (especially area 4), lesions are also found in the vestibular nuclei and cerebellar centers Rarely have lesions been found in the olfactory bulbs in human cases —an important negative finding because it was once thought that the virus invariably entered the human body via the olfactory tract

Incubation Period—This is about ten days but it may be variable ranging from as short as five to as long as thirty five days Average figures place it at twelve to thirteen *days for paralytic cases and nine to ten* days for abortive cases the difference is due no doubt to the fact that the prodromal symptoms in the former (paralytic) may be so slight as to escape notice

Symptoms—With most patients poliomyelitis is a mild illness of short duration But in a certain proportion of those infected the disease is severe and its most serious manifestation occurs—namely myelitis

In a mild *abortive case* the onset is sudden with fever malaise *headache vomiting* and perhaps sore throat—symptoms which may last from a few hours to a few days The child may be restless and somnolent by turns and irritable when aroused and handled Vomiting and headache are characteristic early symptoms Diarrhea is not particularly common (if purgatives have

family the reasons for this in order to allay undue anxiety As the clinical picture of *abortive poliomyelitis* is essentially nonspecific it is obvious that mistakes will be made but too often the story is that a child with an acute illness stays in bed for only a day or two and then returns to play where he perhaps sustains a fall which is again followed by fever and subsequently by paralysis It is important therefore to protect such a patient from trauma during this stage of the disease Any (non emergency) operative procedure particularly tonsillectomy should be postponed in both sick and well children during epidemic times

In the *early febrile* stage one may follow the same measures as are employed in any acute infection but in this disease in particular one should guard the patient from meddlesome therapy and prolong the period of bed rest beyond that which is ordinarily used Bed rest for a week or ten days is advised for abortive cases Preliminary purgation is not advised nor are any procedures which will subject the patient to unnecessary strain The practice of splinting the limbs or back in an abortive case in order to 'rest' these parts and thus prevent paralysis is to be condemned

If hospital facilities are available one must decide early in an epidemic whether to hospitalize all the abortive (potentially paralytic) as well as the paralytic cases Difference of opinion exists on this point The correct procedure depends on local facilities and circumstances As a rule it does not seem wise to attempt to hospitalize all *suspicious* cases during epidemics

Although no specific treatment is today recognized for acute poliomyelitis *convalescent serum* has been widely used and has been regarded (particularly in certain parts of this country) almost as a specific measure No clear cut statistical evidence has come to the author s attention which indicates that children treated with adult or convalescent serum in any stage of the disease do better than do patients who receive either no serum or horse serum of certain types This does not imply however that adult or convalescent serum should never be used

During the *stage of active myelitis* (in which fever is usually present) the most important aspect of therapy is rest—and careful nursing Patients with acute paralysis are treated best in a hospital but care should be exerted that the trip to the hospital be made with a minimum of exertion to the patient If hyperesthesia of the limbs is present the handling and bathing of the patient should be reduced to a minimum For severe pain and restlessness one may give aspirin grains x (0 6 Gm) two or three times a day codeine grain ¼ or ½ (0 015 or 0 03 Gm) or rarely morphine grain ⅙ (0 007 Gm)

Aspects of nursing care are similar to those of an acute infection The diet should be light and fluids freely given an ice bag may help in cases when headaches are severe Moist heat applied to the back and limbs (see under convalescent treatment) is also advised During the early stage of acute myelitis when weakness or paralyses are developing the patient may be allowed to assume in bed whatever position is most comfortable A board can be placed against the foot of the bed against which the soles of the feet may rest so that he can have something to push against in shifting his position

Frequent (daily) *lumbar punctures* have been recommended by some on the theory that the removal of spinal fluid relieves pressure from the neighborhood of the lesion of the cord The efficacy of this form of treatment has however never been proved and there would seem to be a traumatic risk in the procedure

The immediate application of splints in the *stage of early paralysis of limbs* is not advised Protection of the recently paralyzed limb (rather than fixation), and the application of moist heat in order to reduce muscle spasm are the objectives to be sought

Constipation often develops It should not be regarded with alarm although it may be difficult to overcome It usually does not persist for more than a week The use of strong purgatives is not advised

Cases with *bulbar paralysis* require special treatment Owing to difficulty in swallowing secretions accumulate in the pharynx which may interfere with respiration Treatment should consist in postural drainage with frequent shifting of the patient s position by swabbing the throat or (if there are facilities) by suction using an aspirator such as

count is apt to reveal a moderate leukocytosis (10 000 to 14 000) with lymphoid cells ranging from 30 to 55 per cent

Differential Diagnosis—Poliomyelitis is one of the few infectious forms of myelitis It should be considered whenever flaccid paralysis (particularly paralysis without sensory changes) occurs in the presence of fever and in the absence of traumatic or other types of injury to the cord

It can be confused with the summer encephalitides particularly the *equine encephalomyelitides* or *St Louis encephalitis* Serious paralyses of the limbs do not usually occur, however, *in these encephalitides Post-measles encephalitis mumps encephalitis meningo encephalitis* (of undetermined type) *lymphocytic choriomeningitis* and *infectious neuronitis* are conditions that may simulate poliomyelitis

Other conditions which have been confused are the *acute meningitides* (of various types) tuberculous meningitis and rheumatic fever In these conditions the diagnosis is apt to become apparent in the course of time More rarely *acute osteomyelitis trichinosis acute appendicitis* and *lead poisoning* are mistaken for poliomyelitis

Prognosis—During the acute stage predictions as to eventual outcome or effects are risky Extensive paralysis may develop unexpectedly and rapidly even in the absence of fever The height of the fever bears little relationship to the extent of paralysis which may ensue However the duration of fever may be significant for as fever and other signs of acute infection recede the danger of the onset or extension of paralysis lessens

It has been said that in a moderately severe epidemic anywhere up to 70 per cent of the cases are paralyzed but such statements mean little because they depend so much upon criteria of diagnosis In this country prior to 1917 all but a few of the reported cases were designated as paralytic whereas in some recent epidemics both here and in Canada less than 50 per cent were paralytic This ratio differs in different epidemics Furthermore there is apt to be confusion with regard to the diagnosis of non paralytic cases For this and other reasons physicians and health officers should join forces early in an epidemic in order to decide upon various common forms of criteria and action

The case mortality rate will also vary according to diagnostic criteria It may range from 1 to 4 per cent or higher By far the highest mortality occurs in bulbar cases Fifty per cent or more of such patients die

The extent to which patients may hope to recover from *paralysis* in poliomyelitis is also subject to many variables When all the anterior horn cells which control a given area are killed it becomes inevitable that complete loss of power occurs in that region When the cells are but partially damaged perhaps due to pressure or impaired blood supply more or less recovery may be expected There may be no recovery of a single afflicted muscle and there may be a remarkable amount of recovery in a widespread lesion Lovett divided the period subsequent to the acute illness into three stages which are useful in estimating the patient s future (1) the acute stage lasting from the onset of the disease to the complete disappearance of muscle tenderness Roughly this is a matter of several weeks and in some instances much longer (2) the *convalescent stage* from the end of the acute stage to the time of maximum recovery—a period usually placed at two years and (3) the *chronic stage* starting from the end of the convalescent stage and representing the period when residual paralysis is more or less permanent

Treatment—In the acute case the physician must be prepared to withstand strong pressure to do something definite and specific —but there is no specific therapy and no drug therapy known at present which destroys the virus or controls its spread within the body None of the sulfonamide compounds is known to be efficacious

Nevertheless one s responsibility with regard to both mild and severe cases is clear During epidemics all brief febrile illnesses (in which the cause of fever is otherwise unexplained) should be regarded with more suspicion than in ordinary times and such children should be placed under medical observation—because many patients with this disease are for a period of a few days in a stage of *potential paralysis* At the same time one should explain carefully to the

EPIDEMIC ENCEPHALITIS

(Encephalitis Lethargica Epidemic Neuraxitis Epidemic Stupor Type A Encephalitis [Japan], Economo s Disease)

Definition —Epidemic encephalitis is an epidemic infectious malady causing both diffuse degenerative and disseminated inflammatory changes in the central nervous system and its coverings characterized clinically by a marked diversity of symptoms in different cases and in successive stages of the same case partly because of variations in the intensity of the infection partly because of differences in localization of the scattered inflammatory foci It is unfortunate that the name *epidemic encephalitis* has been chosen to designate this disease because at least one other type of encephalitis the St Louis type also occurs epidemically

History —The disease is probably not new though it has become generally known to the medical profession since the pandemic broke out in the winter of 1916–1917 Economo carefully described the disease at that time and called it lethargic encephalitis The noma" in the early nineties of the last century the "sleeping sickness" and ophthalmoplegia that were observed during the influenza epidemic of 1712 may have been the same disease Even the last pandemic may have begun before 1916 because Cruchet in Bordeaux states that he observed cases as early as 1915 During 1917 an epidemic occurred in Australia, reported by Breinl as a "mysterious disease" Economo believed that it was epidemic encephalitis In 1918 encephalitis became prevalent in France Netter recognizing it as an "Encéphalite lethargique epidémique" and in the spring of the same year the disease was met with in epidemic form in 51 sanitary districts in England The first case to be reported in the United States was observed in New York City in September 1918 Shortly afterward the malady began to appear in and to be reported from various parts of the United States and Canada In the first Vienna epidemic (1916–1917) the prevailing type (as in the epidemic in France in 1918) was the somnolent-ophthalmoplegic though there were also examples of the Parkinson like the hyperkinetic and the psychotic syndromes In the English epidemic of the same year bulbar paralytic types were common (at first supposed to be botulism) as were also Parkinson like and catatonic types (hence the name epidemic stupor") In the epidemic in Germany in 1919 the choreiform type the Parkinson like type and the tabetiform type (with pupillary disturbances hypotonia, and areflexia) were described In the great epidemic that began in Italy in 1919–1920 and spread over Austria and Germany the hyperkinetic-myelitic forms (choreiform myoclonic) predominated In America a great variety of types has been encountered though the somnolent ophthalmoplegic were more abundant at first later on the cases characterized by Parkinson like and hyperkinetic syndromes were more frequently seen This large epidemic widespread throughout the world continued from 1915 to 1925 At present only sporadic cases are encountered

Epidemiology —Although it has been assumed that the nasopharynx is the portal of entry the manner in which the virus is transmitted is not known In favor of the idea of contact infection is the fact that incidence among physicians has been exceptionally high Though instances of house infection of conjugal infection or of spread from one person to close companions have been few some have been reported Thus epidemic outbursts have occurred in England in institutions for young females and several children born of parents suffering from the disease have been infected No age is exempt Incidence appears to be greatest however between ten and forty five years of age thus differing from poliomyelitis in which the majority of those affected are children under ten years of age and from the St Louis type of encephalitis in which most of the people affected were more than forty five years old About three males are attacked to two females Occupation appears to exert no special influence upon the incidence of the disease Epidemic encephalitis is commonest during the winter and spring months and in this respect is different from poliomyelitis and the St Louis type of encephalitis which occur most frequently in the summer

Etiology —The cause of epidemic encephalitis is not known but there are reasons to believe that the etiologic agent is a filtrable virus The idea that a streptococcus or that a neurotropic strain of herpes simplex virus is responsible is not substantiated by experimental facts The conflicting views regarding the etiology of the disease are well presented in a paper by Zinsser in the Archives of Pathology 6 271 1928

Morbid Anatomy —On macroscopic examination of the nervous system areas of hyperemia in the meninges may be seen the vessels on the surface of the brain are engorged and on section the vessels appear prominent especially in the basal ganglia midbrain and pons where minute hemorrhages are sometimes visible On microscopic examination two changes can be made out one degenerative the other inflammatory and infiltrative One or the other predominates according to the stage of the disease at the time of death The degenerative process manifests itself by the destruction and

those used in an operating room Atropine (grain 1/100) may be of value in reducing the amount of secretion If swallowing is impaired, fluid salt and nutriment should be administered either by clysis or intravenously or by proctoclysis The amount of fluid administered is dependent on the age size and general condition of the patient

When *respiratory failure* occurs it is not always easy to decide which part of the respiratory system is involved If paralysis of the respiratory center of the medulla occurs little can be done other than the administration of oxygen and carbon dioxide in a 95 per cent and 5 per cent mixture respectively

The *Drinker respirator* has been widely used in cases of paralysis due to weakness of the respiratory muscles This is often an emergency procedure and once the patient has been put in the respirator much time and money may be spent before he can be removed Every effort should be made on the part of physicians and nurses (as well as hospital mechanics) to acquaint themselves with the technical details and responsibilities in operating the respirator before it is actually used The directions by Wilson are recommended

Early Convalescence—Patients should have orthopedic supervision in this stage and the advice of specialists for there are many conflicting points of view and one cannot be dogmatic about the treatment of paralysis The introduction of Miss Kenny's principles is a forward step which has done much to disparage the rigid fixation of all paralyzed or weakened limbs in splints The application of moist heat to the limbs and body and the early re education of muscles are measures now superseding the older methods This does not mean that physicians or surgeons untrained in orthopedics should be consulted any the less or that untrained nurses or attendants should attempt to apply any aspects of the convalescent therapeutic regime

Prophylaxis—Inasmuch as the mode of spread is unknown it is difficult to devise rules for prevention There are no rigid directions Isolation of patients as usually practiced seems to be ineffective in controlling the spread of the disease In the early stages of an epidemic it is wise to seek the counsel of the local health officer immediately so that a *uniform* plan may be adopted in which all physicians may join There are a few simple principles to follow (1) to recall that abortive cases may be infectious as well as the paralytic cases (2) to discourage the eating of uncooked food to which flies or many other sources of contamination may have had ready access (3) to discourage swimming in filthy ponds or in areas either grossly polluted by sewage or crowded with children among whom there may be carriers (4) to put a ban on tonsillectomy operations and other minor operations which may be postponed during the epidemic period

Injections of antisera (convalescent or adult blood) as a form of passive immunization have been suggested but the practical difficulties are great and their general use is not recommended

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sist In some cases marked mental deterioration occurs and may be mistaken for general paresis Manic and melancholic states have been observed and less often a condition simulating dementia praecox has been seen

Other Types —Many other types have been described including a poliomyelitic type with lower motor neuron paralyses a posterior root ganglion type with herpes and radicular neuralgias or anesthesias a tabetic type with ataxia and sluggish pupils an epilepto maniacal type a cataleptic type with statuesque attitudes and an amyostatic kinetic type in which there is seen apathy rigidity akinesis without paralysis great slowing of movements amimic facies and sometimes, tremor

Aberrant Forms and Formes Frustes —Very peculiar aberrant forms of the disease may occur which simulate some other malady often of some part of the body other than the nervous system Examples of such aberrant forms are the intestinal types (Massari) the dyspneic types (Economo) and the fulminant cases that terminate fatally after a few hours (*Encephalitis siderans*) In one case observed by Barker and Sprunt tetany developed as the result of a post encephalitic paroxysmal hyperpnea Abortive forms and *formes frustes* are undoubtedly very common during epidemic periods nuclear paralyses in the domain of the cerebral nerves radicular neuralgias deafness vertigo or trismus may be the only manifestations

Second Stage —In the second or pseudo psychoneurotic stage there are many subjective complaints—headache insomnia dizziness fatigability irritability and restlessness—often without demonstrable objective findings of organic nervous disease The symptoms may however persist for months or even for years after which the symptoms of the third stage may appear Occasionally the symptoms of the third stage follow almost immediately upon those of the first In children the second stage may be marked by alterations of character and oddities of behavior (Hohman)

Third Stage —In the third or chronic stage peculiar motor vegetative and psychic symptoms make their appearance The disturbances of motility are like those of the Parkinson syndrome with or without tremor Among the commoner vegetative disturbances are sialorrhea dacryorrhea and seborrhea On the mental side there may be intellectual and emotional torpor with marked slowing of thought

Diagnosis —When the disease is epidemic and typical cases are occurring, encephalitis should always be suspected in puzzling cases of fever somnolence or delirium Signs of meningeal irritation external or internal ophthalmoplegia neuralgias or paralyses in cerebral nerve domains or pathologic drowsiness associated with fever or leukocytosis should always excite suspicion On lumbar puncture the cerebrospinal fluid may be normal but often there is an increase in the amount of globulin a slight increase in the number of cells and an increased or normal amount of sugar changes that are strongly corroborative of encephalitis when the Wassermann reaction is negative Helpful in diagnosis are the acute onset of nervous symptoms with evidence of predominant involvement of the gray matter the paucity of massive paralyses in contrast with an abundance of disturbances of multilocular origin in unusual combinations the tendency to transitory pareses rather than to complete paralyses and the nonsystematic nature of the observable symptoms

Among the conditions to be differentiated from epidemic encephalitis are botulism nervous forms of influenza epidemic cerebrospinal meningitis tuberculous meningitis, uremia cerebral hemorrhage cerebral embolism cerebral thrombosis cerebrospinal lues brain tumor acute anterior poliomyelitis multiple neuritis multiple sclerosis St Louis type of encephalitis acute lymphocytic choriomeningitis and postinfection encephalitis

Prognosis.—The mortality varies in different epidemics It probably amounts to 20 or 30 per cent if the outspoken cases only are considered the death rate would doubtless be lower if atypical and rudimentary cases were to be included Of the patients who do not die a large number recover rapidly others remain more or less invalid for from six months to two years still others are permanently disabled because of the severe symptoms of the third stage

Treatment —In the acute stage rest in bed isolation protection from avoidable

the indistinct staining of nerve cells The inflammatory change appears as scattered patches of infiltration especially in the gray matter with accumulation of small and large mononuclear cells and plasma cells in the sheaths of the vessels and in the perivascular spaces The nervous tissues themselves show also patches of diffuse infiltration with the same type of cells There are signs of neuronophagia Proliferation of the glial elements is seen in the areas of inflammation which tend to be most abundant in the basal ganglia midbrain and pons In chronic relapsing cases lesions of different ages have been demonstrable at autopsy Certain workers are inclined to believe that there is a systemic infection prior to the involvement of the central nervous system but proof of this view remains to be obtained

Incubation —It is believed that the incubation period in most instances is four to fifteen days

Symptoms —The mode of onset has varied markedly not only in different epidemics but also among cases in the same epidemic and may be either sudden or gradual The first symptoms may be those of an acute respiratory infection with headache malaise and fever In the Vienna epidemic of 1916–1917 there was usually a forestage with symptoms of slight meningeal irritation before the somnolence and paralyses of the eye muscles appeared In the United States the onset in some cases was sudden with severe pains in the head fever and delirium in other cases it was more insidious with fever diplopia and slight mental confusion or with sensory disturbances and pareses in cerebral nerve domains In a few cases the disease has been ushered in by a stroke of apoplexy an epileptiform attack a sudden syncope or a severe vertigo

First Stage —The clinical picture of the fully developed disease varies greatly A large number and variety of symptoms may be met with in the most diverse combination and sequence Experience with many cases indicates that the manifestations may simulate those of almost every well known neurologic symptom complex thus making differential diagnosis sometimes very difficult Certain syndromes however are more common than others and merit especial mention

In the first stage we meet most often with either (1) a somnolent ophthalmoplegic syndrome, or (2) an irritative hyperkinetic syndrome either choreiform or myoclonic

Somnolent Ophthalmoplegic Type —A triad of symptoms—fever somnolence, and ophthalmoplegia—characterizes the lethargic type of encephalitis After a brief initial stage with fever and symptoms of meningeal irritation the patient becomes drowsy and exhibits paralyses of the eye muscles Sometimes there are other symptoms—general rigidity paralyses in the limbs or head symptoms of motor irritation and delirium or other mental disturbances The fever may be slight or severe many afebrile cases have been noted

Hyperkinetic Types —In the hyperkinetic type following an initial stage of fever and excitement severe symptoms of motor irritation appear in the form either of choreiform (or choreo athetotic) movements or of myoclonic contractions In the choreiform variety there are involuntary and irregular movements of the automatic associated type these may be general unilateral or local in distribution and may vary much in intensity Occasionally the movements of an extremity are slow and rhythmical, recurring regularly eighteen or twenty times per minute (bradykinetic oscillation of Marie and Levy) The choreiform types are believed to be caused by lesions of the neostriatal system of neurons (Ramsay Hunt) In the myoclonic variety there is marked irregular twitching of muscles or parts of muscles probably due to irritative lesions in the spinal cord Bilateral twitching of the abdominal muscles may be an early sign of encephalitis (T F Reilly) Less common is a bilateral synchronous myoclonia during which the muscles of the trunk and of the proximal portions of the extremities contract fifty or sixty times per minute (Hamill) Persistent hiccup is common

Psychotic Types —Psychoses of the organic reaction type may dominate the clinical picture Mental grasp is impaired memory defects are evident orientation as to time place and persons is faulty and attention is disordered (Kirby) In the more acute forms delirium may alternate with pathologic drowsiness or stupor Emotional disturbances are common and tend to per

tis which is most prevalent in the winter and spring No age is exempt but the high est incidence is in individuals more than forty five years of age while Economo's en cephalitis usually attacks people ten to for ty five years old and poliomyelitis is princi pally a malady of children less than ten years of age In the St Louis 1933 epidemic the attack rate was considerably higher among inhabitants of the suburbs than among those in the city proper

Etiology —The disease is caused by a small filtrable virus possessing a diameter of 20 to 30 millimicra The agent has not been cultivated in a lifeless medium but has been propagated in one containing viable susceptible cells Albino mice and rhesus monkeys are susceptible hosts the former is the one of choice for the demonstration of virus in suspected material and for the per formance of neutralization tests used in ar riving at a diagnosis

Incubation —It has been estimated that incubation periods range from four to twen ty-one days

Morbid Anatomy —Edema vascular con gestion and small hemorrhages are usually evident upon gross examination of the brain and cord Microscopic examination reveals an infiltration of the meninges with lympho cytes plasma cells large mononuclear ele ments and an occasional polymorphonuclear cell In the brain and cord are evidences of an acute inflammation *e g* vascular con gestion small hemorrhages cellular infiltra tion perivascular cuffing degeneration of nerve cells neuronophagia and proliferation of glial elements The focal accumulations of cells around the blood vessels are limited to the Virchow Robin spaces and for the most part consist of elements with the morpho logic characteristics of lymphocytes In many instances there are foci of mononu clear cells bearing no relation to blood ves sels these seem to consist of lymphocytes and glial elements (oligodendroglia and microglia)

Symptoms —The fact that the clinical picture varies tremendously can be ex plained upon the basis of differences in the severity of the infection and the localization of lesions in the brain and cord According to Hempelmann the cases may be placed in three large groups

Group I —Patients in this group exhibit an abrupt onset without prodromal symp-toms High fever nausea, vomiting head ache, vertigo nuchal rigidity, Kernig s sign lethargy, difficulty with speech, ataxia, men tal confusion and tremor of tongue, lips or hands are the most common signs and symp-toms All the patients are not lethargic par alyses are not common and when they do occur are usually of the spastic type in volvement of the eye muscles is extremely rare a state of affairs very different from that met with in lethargic encephalitis The abdominal reflexes are usually absent while the deep reflexes tend to be exaggerated in stead of diminished Constipation is com mon The pulse is usually proportional to the temperature but a bradycardia may occur

The spinal fluid may be under increased pressure is free from ordinary bacteria, con tains a normal amount of sugar an increased amount of globulin and an increased num ber of cells consisting chiefly of lymphocytes and other mononuclear elements The num ber of cells in the fluid tends to be higher than that encountered in epidemic encepha litis The white blood count may be normal or show a leukocytosis

As the patient s condition improves the temperature falls by lysis and in most in stances reaches the normal level within seven to ten days in a few cases however the fever persists for from four to six weeks

Group II —In this group of cases a stage of invasion lasting from one to four days and characterized by headache general ma laise abdominal pains chilly sensations fever generalized muscular pains sore throat and a mild conjunctivitis accom panied by photophobia precedes the picture of encephalitis which after its development is similar in all respects to that described for Group I

Group III —The third group consists of mild or abortive cases exhibiting only head ache and fever of undetermined cause which would be missed in the absence of an epi demic and incorrectly diagnosed without the aid of a lumbar puncture

Diagnosis —Epidemics of the St Louis type of encephalitis are distinguishable from those of Economo s (lethargic) encephalitis but frequently individual cases of the for mer malady cannot be differentiated from

optic acoustic and tactile stimuli, skilful nursing restriction to a liquid diet and tepid sponging are beneficial Repeated lumbar punctures or hypertonic solution of glucose given intravenously frequently relieve the headache and diminish drowsiness of the early stages, especially when the pressure of the cerebrospinal fluid is increased Water should be given freely by mouth or by continuous Murphy drip if the patient be difficult to arouse For the nocturnal restlessness the bromides or barbital in hot milk may be useful In the hyperkinetic states and in violent delirium sedatives such as *paraldehyde and Schlesinger s solution* are required In spite of claims to the contrary there is no evidence that any of the vaccines or sera used in the treatment of the disease are of value

After the acute stage is over care should be exercised to avoid relapses Convalescents should be closely watched and their activities directed meticulously for a long time A prolonged period of rest after the acute stage is over may do much to prevent the development of the much dreaded third stage

The therapeutic resources of the physician will be severely taxed in the management of patients suffering from the symptoms of the third stage of the disease For the asthenia general upbuilding measures are helpful some patients seem to be benefited by adrenal residue (5 to 10 minims after each meal) For tremor and for parkinsonian rigidity doses of increasing size of hyoscine hydrobromide ($\frac{1}{200}$ to $\frac{1}{60}$ grain) are valuable or tincture of stramonium may be tried Large doses of sodium cacodylate given intravenously every four or five days have been much lauded In Vienna intravenous injections of sodium iodide have been found to be beneficial To promote recovery from paralyses massage and galvanism may be employed For sialorrhea atropine or hyoscine may be given in full doses Patients with severe psychotic symptoms or exhibiting anomalies of behavior may have to be cared for temporarily or permanently in a closed institution

This chapter was originally written by Dr L F Barker and the revised form of this edition is with certain exceptions identical with that prepared by him Dr Barker was kind enough to permit the use of his material in this manner

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ST LOUIS TYPE OF ENCEPHALITIS

Definition—The St Louis type of encephalitis is a virus disease characterized by signs and symptoms referable to the central nervous system and its meninges but differing from epidemic encephalitis in certain important respects It may occur either epidemically or sporadically

History.—In the summer of 1933 in and around St Louis more than 1000 cases of encephalitis occurred The epidemic as a whole exhibited characteristics different from those observed in epidemics of Economo s disease or epidemic encephalitis Muckenfuss Armstrong and McCordock and Webster and Fite quickly demonstrated that the epidemic was caused by a filtrable virus previously unrecognized Soon it was also realized that the disease had occurred in the United States prior to 1933 particularly in Paris Illinois Furthermore it has been shown that the malady is now endemic in America cases having been reported each year since 1933

For many years Japanese workers have been aware of an epidemic summer encephalitis different from Economo s disease or epidemic encephalitis (Type A) and have designated it as Type B encephalitis In fact up to 1929 13 epidemics of the malady had been recorded *This encephalitis is immunologically different from the St Louis type*

Epidemiology—The mode of spread is not known The malady occurs most frequently during the summer months in this respect it differs from Economo s encephali

injections of emulsions of fresh normal rabbit brain, have produced in monkeys a perivascular demyelination manifested clinically by ataxia and paralyses

Incubation —In view of the indecision regarding the etiology of the disease it may seem inappropriate to speak of an incubation period Regardless of the cause of the encephalitis one cannot deny that there is a definite relation between it and the primary infections In any event there is a comparative constancy of incubation—that is of the period which elapses between the onset of the primary disease and the occurrence of the complicating encephalitis In the case of postvaccinal encephalitis the incubation period in most instances lies between the ninth and thirteenth days the most favored day being the eleventh In the case of antirabic vaccination the encephalitis or myelitis usually comes during the second half of the Pasteur treatment or after it has been completed In the case of measles the incubation period is not very constant but as a general rule the encephalitis follows the appearance of the rash at variable intervals—usually it comes after the defervescence and at times the patient may have fully recovered from the measles

Morbid Anatomy —Pathologic changes are found in both the white and gray matter of the brain and cord and are characterized by a minimal involvement of nerve cells and a perivascular infiltration or accumulation of cells accompanied by a destruction of myelin The perivascular collections of cells are not limited to the Virchow Robin spaces and consist largely of altered glial elements undergoing proliferation many of which become phagocytic and take up large amounts of fat and degenerated myelin This pathologic picture is decidedly unlike that seen in the encephalitides caused by viruses on the other hand in many respects it is similar to that seen in acute multiple sclerosis and allied conditions

Symptoms —There are two main types of the disease the encephalitic and the myelitic the former is more common in postvaccinal encephalitis the latter is seen most frequently during antirabic vaccination while both types occur with almost equal frequency after smallpox Under such conditions it is to be expected that the clinical picture will vary and that the form it takes will depend on whether the brain or cord is predominantly involved

The onset of the disease if not abrupt is rarely insidious and is manifested in the encephalitic cases by pyrexia headache vomiting and drowsiness—cardinal symptoms constantly present in severe, and rarely absent in mild cases they may be the only symptoms present even in fatal cases' Photophobia irritability, delirium general or local convulsions, trismus, strabismus incontinence of urine, extensive paralyses (spastic at first and then flaccid) or transient weakness of muscles incoordination and ataxia are symptoms that may occur Kernig's sign may be present the deep and superficial reflexes are variable In the myelitic cases symptoms caused by mild or severe involvement of the cord such as paralyses anesthesias paresthesias and disturbances of sphincter control are observed

The spinal fluid may be under increased pressure is sterile and may contain an increased number of cells which are usually mononuclear elements the amount of sugar is within normal limits

Diagnosis —The clinical picture of postinfection encephalitis is at times not unlike that caused by certain known viruses for example, the St Louis encephalitic virus Consequently, it is important to remember that all cases of encephalitis occurring in the wake of infectious diseases are not necessarily postinfection encephalitis In certain instances they undoubtedly represent other types for example some cases of encephalitis following antirabic vaccination are in reality rabies and some that occur after measles are of the hemorrhagic rather than the demyelinating type Often it is difficult and at times impossible by means of clinical observations alone to differentiate postinfection encephalitis from the other types In view of this fact a history of an encephalitis during convalescence from a virus malady usually results in a diagnosis of postinfection encephalitis As a rule such a diagnosis is correct but not always At present a definite diagnosis of postinfection encephalitis can be arrived at only by means of a careful examination of the brain and cord which should show a characteristic perivascular demyelination

those of the latter by means of clinical or pathologic observations alone Neutralization and complement fixation tests aid in arriving at a correct diagnosis

Prognosis—About 20 per cent of the patients die the mortality rate is much higher in old people than it is among the young Those who recover do so quickly as a rule and are not usually bothered by troublesome or disastrous sequelae

Treatment—Treatment is symptomatic

THOMAS M RIVERS

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POSTINFECTION ENCEPHALITIS

(Acute Disseminated Encephalitis Acute Perivascular Myelinoclasis Postvaccinal Encephalitis Postmeasles Encephalitis)

Definition—Postinfection encephalitis is an acute malady of the central nervous system characterized by perivascular demyelination exhibiting itself as a rule in patients who are convalescing from infectious diseases particularly those caused by viruses or in those who are being vaccinated against virus maladies such as smallpox or rabies In certain instances the disease manifests itself in the absence of a history of preceding infection

History.—For a long time it has been known that an involvement of the central nervous system may complicate the picture of smallpox and measles In 1874 Westphal recorded descriptions of pathologic changes observed in the cords of patients who had died with nervous manifestations developing during an attack of smallpox and in 1886 Barlow and Penrose gave an account of a similar case that arose during the course of measles Soon after the initiation of vaccination against rabies it was realized that an occasional individual receiving the injections met with paralytic accidents which at times resulted in death In 1907 Comby described a case with involvement of the central nervous system as a complication of jennerian prophylaxis this observation was followed by a similar one made by Turnbull in 1912 Although isolated cases of the nature just mentioned had been described from time to time it was not until the outbreak of postvaccinal encephalitis in Holland England, and other countries in 1922 that attention was focused on them As the result of extended clinical pathologic, and experimental observations the tendency at present is to consider this type of nervous accident following in the wake of acute infections as a clinical entity

Epidemiology—The disease has been shown to occur during the course of and after vaccination against rabies and smallpox and during or after an attack of smallpox measles German measles varicella or influenza a few cases have been reported in which no history of a preceding infection was obtained The incidence varies from year to year being lower now after jennerian prophylaxis than it was in 1922–1925 It is not distributed uniformly throughout the population of a country nor are the inhabitants of all countries equally affected No age is exempt the malady occurs however more frequently in children than in infants and adults There is no evidence that the disease is contagious

Etiology—The cause of postinfection encephalitis is not known nor has the malady been transmitted from man to experimental animals The three most prevalent ideas regarding the etiology are (1) the viruses that cause the primary disease *e g* smallpox measles etc also give rise to the complicating encephalitis (2) a latent neurotropic virus is activated by the primary disease processes (3) inasmuch as the encephalitis occurs during convalescence from some infectious malady certain workers have suggested that it is an expression of allergic phenomena There is no convincing evidence that any of these ideas is correct Moreover it seems unlikely that the direct action of a virus is the cause of the disease because no virus is known to produce a perivascular demyelination similar to that seen in this disease Furthermore Rivers and his co workers by means of repeated intramuscular

The final link in the chain of epidemiologic circumstances to be accounted for is the mechanism whereby the virus survives from one season to the next Recent experimental work of Syverton and Berry suggests an explanation for this They showed that the tick *Dermacentor andersoni* could be infected by feeding on an infected animal This insect harbored the virus throughout its life and could pass it on to a succeeding generation through the ova

Prevention of the Disease in Horses.—Shahan and Giltner showed that a vaccine could be prepared by treating an emulsion of infective horse brain with formalin Although some evidence of protection was obtained with this preparation the results were not entirely satisfactory In 1935 Higbie and Howitt showed that the developing chick embyro could be infected with this virus In 1938 Beard Finkelstein Sealy and Wyckoff prepared a vaccine by formalinizing a suspension of infected chick embryo tissue Such tissues were found to contain a much higher content of virus than infective horse brain This material has been widely used during the past two years Vaccination of horses and mules is achieved by subcutaneous injection at weekly intervals of two doses of 10 cc each of the vaccine of triturated chick embryo tissue treated with 0 4 per cent formalin Experimental and field studies have shown that this method is very effective Practical sanitary measures should of course be employed such as screening stables and removing horses and mules from pastures after dark

The Disease in Man—Meyer in 1932 described three cases of encephalitis in individuals having contact with sick horses which he suspected might be due to the virus of the equine disease No proof for this suspicion was obtained however by biologic test

During the summer of 1938 an epidemic of the eastern variety of the disease occurred among horses in southeastern Massachusetts During this time and in the same area an unexpected number of human cases of encephalitis occurred These were proved by Fothergill Dingle Farber and Connerley and by Webster and Wright to be caused by the equine virus by isolating the infectious agent from the brain tissue of fatal cases

There were about 40 human cases in this outbreak with a mortality of 65 per cent The majority of cases occurred in young children 70 per cent of them under ten years of age During the summer of 1941 more than 3000 cases occurred in the north central states

The onset of the disease was usually sudden particularly in young children The temperature rose rapidly to 103° F to 105° F and generally remained at a high level during the course of the disease In some cases the disease was ushered in by a convulsion Repeated convulsions occurred during the course of the illness in many patients Deep coma occurred rapidly and persisted throughout the acute stage of the illness Nuchal rigidity, stiffness of the back and positive Kernig s sign were usually present Many of the younger patients developed a peculiar edema about the face and upper extremities In some of the older patients the onset was more gradual

Certain of the laboratory findings were of importance particularly during the first few days of illness A leukocytosis was always present The cerebrospinal fluid was under increased pressure and contained an increased amount of protein and a normal content of sugar The cell count varied from 200 to 2000 per cu mm Of considerable importance was the fact that from 60 to 90 per cent of the cells were polymorphonuclear leukocytes

In fatal cases death occurred at variable times during the course of the disease most commonly during the first few days In the few patients who recovered the acute phase of the illness terminated by lysis six to ten days after the onset The majority of the patients who survived were left with severe mental and physical damage

It must be emphasized that a diagnosis of encephalitis in man due to the virus of equine encephalomyelitis cannot be made on the basis of the clinical findings It may be confused with other types of acute infectious encephalitis such as polioencephalitis and St Louis encephalitis An increase in the incidence of encephalitis in man in an area where an epidemic of the disease in horses and mules is in progress should lead one strongly to suspect the equine type of the disease Virus was not isolated from any of

Prognosis—Ten to 50 per cent of the patients die the mortality rate is much higher in postvaccinal encephalitis (50 per cent) than it is in postmeasles encephalitis (10 per cent), the rate also varies from year to year in the same type being considerably lower now in postvaccinal encephalitis than it was in 1922–1925 The patients that recover usually do so completely, sequelae occasionally occur, and it seems that they are more frequent in cases developing after measles than in those following jennerian prophylaxis

Treatment—The treatment is symptomatic Headache may be relieved by repeated lumbar punctures and the intravenous administration of hypertonic glucose solution Definite evidence is lacking, in spite of claims to the contrary that convalescent measles serum etc are of therapeutic value

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EQUINE ENCEPHALOMYELITIS

The Disease in Horses—This disease has undoubtedly been present among horses and mules in this country for many years having been diagnosed as botulism forage poisoning and so on In 1931 it was proved to be caused by a filtrable virus by Meyer Haring and Howitt during the course of their studies of an epidemic in the San Joaquin Valley in California Since then our knowledge of its extent epidemiology transmission prevention and so on has accumulated rapidly

In 1933 an epidemic occurred along the seacoast of Virginia and New Jersey which was shown by Ten Broeck and Merrill to be due to a virus immunologically distinct from that causing the disease in the West. The eastern disease moreover is more severe than the western, with a considerably higher mortality rate (about 90 per cent as compared to 25 to 30 per cent) The two diseases are referred to as the eastern and western types of equine encephalomyelitis The geographic distribution of each type appears to be strictly limited by the Appalachian Mountains

The first important clue to the mechanism of spread of epidemics was provided by Kelser's classic experiments in which he demonstrated that the virus could be transmitted by the mosquito *Aedes aegypti* Subsequently Kelser as well as other investigators has shown that other mosquitoes including *A sollicitans A cantator A vexans A taeniorhynchus A dorsalis A nigromaculis* and *A albopictus* may transmit the virus It is of interest that the *Anopheles* mosquitoes fail to transmit the virus Recent experiments have demonstrated transmission of the virus by *Culex tarsalis* The mosquito transmission of the virus adequately accounts for the spread of the disease in a particular area however it does not explain the sudden appearance of the malady in widely separated areas

Giltner and Shahan showed that pigeons were susceptible to infection following intracerebral inoculation of the virus and suggested that birds may play a role in the epizootiology of the disease Other investigators demonstrated that additional species of birds were susceptible During the course of the 1938 epidemic in Massachusetts Tyzzer Sellards and Bennett isolated the virus from pheasants dying in their natural state and Fothergill and Dingle isolated the virus from a pigeon under similar circumstances These findings clearly implicate birds in the epidemiology of the disease and explain its spread to widely separated areas Indeed it appears likely that the malady is primarily a disease of birds and that man and horses are accidental secondary hosts

rather generally throughout the United States Many thousands of cases are known to have occurred in Scandinavia and Finland within the past few years

In all countries where the disease has been observed there is a very definite seasonal occurrence it being met with almost exclusively during the warm months Figures from different sources show a rather wide variation in the age incidence of the disease but it seems probable than 50 per cent or slightly more of all cases are in children under fifteen years and 80 per cent under thirty The two sexes appear equally susceptible

Many careful studies of epidemics have failed to produce any evidence that contagion is transmitted by water food or insects On the other hand abundant data have accumulated which seem to indicate conclusively that the virus is spread by contact infection The incubation time is quite definitely established as from two to four days We have no accurate knowledge of possible immunity but no case of reinfection has been recorded

Etiology and Pathology —Exhaustive etiologic studies have failed to determine the exact nature of the disease There is some evidence however that the infection is due to filtrable virus presumably present in the nasopharyngeal secretions Since no post mortem examination has ever been made in a case of this disease we have no knowledge of its pathology Presumably the essential lesions of the disease are in the diaphragmatic pleura but their nature can only be a matter of conjecture Many patients have undergone a laparotomy with the mistaken diagnosis of an acute abdominal emergency but in no instance has any abnormality been observed in any of the abdominal organs or peritoneum

Symptoms —Prodromata are rarely present The onset is abrupt and often alarming because of the intensity of the symptoms and attending collapse This is especially true in children The earliest symptom is pain and throughout the course of the disease is its chief manifestation The seat of the pain is invariably at the level of the attachment of the diaphragm most commonly high in the epigastrium but often on one or both sides of the lower thorax anteriorly It may shift to some degree from day to day Its character varies considerably from a dull pressure or distress to the most acute type of paroxysmal seizure Pain is particularly associated with the respiratory function and is intensified by sneezing coughing exercise laughing and deep breathing Relief from the pain is naturally sought in a protective splinting of the lower thorax which can usually be accomplished by some fixed position and shallow breathing If able to move about the patient walks with the body bent toward the affected side and held in a fixed position while the gait is slow and painful A moderate degree of tenderness can often be made out over the painful areas and there is nearly always marked sensitiveness to deep pressure in the upper epigastrium The patient may also suffer from localized pain over small areas with cutaneous hyperesthesia in other parts of the body such as the lower abdomen lumbar region and over the shoulders back and sides of the neck

Fever invariably accompanies the pain and within a few hours may reach a maximum of 104° or even 105° F dropping to normal at the end of twenty four to forty eight hours or in mild cases still more promptly With any recrudescence of symptoms the temperature again rises and in cases running a severe course a continuous irregular fever sometimes persists for ten or more days The pulse rate at onset may be moderately elevated (90–100) Because of the pain the depth and rate of respiration are minimized In rare cases with great respiratory embarrassment a light degree of cyanosis has been noted Frontal headache is a frequent and important symptom but very variable in its intensity and of short duration Pain in the back and legs is rather common in children but rare in adults Chills in some form are present in the early stages in 50 per cent of cases Prostration may be extreme during the height of the pain but the attack is of such short duration that with relief of pain the rebound is surprising A particularly distinctive feature of epidemic pleurodynia is the marked tendency to recurrent attacks at intervals of one or two days (in our series 63 per cent)

Gastro intestinal symptoms play but a small role in adults but a prominent one in

the Massachusetts cases by inoculation of animals with blood or cerebrospinal fluid

A diagnosis can eventually be established in the majority of cases by certain biologic tests The most important of these is the isolation of the virus from the brain tissue of acute fatal cases obtained at necropsy It is advisable to take small portions of brain tissue from various regions in the brain and brain stem The tissue is emulsified in physiologic salt solution and inoculated intracerebrally into white Swiss mice or guinea pigs If virus is recovered it can be identified by immunologic tests (protective tests in actively immunized animals or by serum neutralization tests) If it is impossible to inoculate animals immediately brain tissue can be preserved in the ice box in a mixture of 50 per cent neutral glycerin in buffered Tyrode solution It is very important to preserve such material in a buffered mixture since the virus is inactivated very rapidly by the developing cadaveric acidity Histologic examination is of course of great value in diagnosis

In cases with a prolonged illness and in convalescent patients a diagnosis may be made by neutralization tests with patients serum Neutralizing antibodies appear in seven to ten days after the onset of the illness

Treatment —There is no specific therapy for this disease Treatment is entirely symptomatic consisting of the administration of sedatives for the control of convulsions administration of fluids parenterally and food by gavage during the period of coma

Prevention of the disease in man if an epidemic occurs should consist largely of sanitary measures Houses and particularly sleeping quarters should be screened against mosquitoes and children should not be allowed outside after sundown A vaccine similar to that for horses could be developed for use in man However the infrequency of the disease in the latter does not justify large scale vaccination The vaccination of laboratory personnel is indicated since Fothergill Holden and Wyckoff have reported a fatal case resulting from accidental infection in a laboratory

LeRoy D Fothergill

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EPIDEMIC PLEURODYNIA

(*Bornholm Disease Myalgia Epidemica Devil s Grip Epidemic Transient Diaphragmatic Spasm Epidemic Diaphragmatic Pleurodynia*)

Definition —Epidemic pleurodynia is an acute infectious and highly contagious disease which occurs largely in epidemic form and is characterized by pyrexia headache and very severe paroxysmal pain in the region of the attachment of the diaphragm The attack is of brief duration but tends to one or more relapses

History —The disease was first observed in Iceland by Finsen in 1856 and again in 1863 but his account of these observations was not published until 1874 He recognized the epidemic nature of the disease and first used the designation pleurodynia

In 1888 Dabney recorded an Epidemic resembling Dengue in Virginia which was the first observation of pleurodynia to be made in America Reilly in 1889 and 1921 published accounts of small groups of cases under the designation of intercostal neuritis and unusual pain syndrome which were undoubtedly examples of the same disease

Incidence —The disease has a very wide geographic distribution and there is increasing evidence that it occurs in epidemics

THE RICKETTSIAL DISEASES

INTRODUCTION

The rickettsial diseases of man are world wide in distribution and in general may be defined as self limited specific diseases transmitted by arthropods and characterized by continued fever a rash and a positive Weil Felix reaction The causative micro-organisms —*Rickettsiae*—may be regarded as pathogenic representatives of minute bacterium like micro-organisms widely distributed among arachnids (ticks mites and spiders) and hexapods (insects) including many non blood sucking species The pathogenic rickettsiae exhibit numerous differences but all are gram negative stain feebly with aniline dyes and behave as obligate intracellular parasites in arthropods and in susceptible animals Three groups of human rickettsial diseases of man are now well established the typhus louse and flea vector group the Rocky Mountain spotted fever or tick vector group and the tsutsugamushi or mite (*Trombicula*) vector group In general the distinctive lesions of these diseases are found in relation to small blood vessels chiefly of the skin and central nervous system but also in the genitalia and other organs Trench fever is usually grouped with the rickettsial diseases because it is transmitted by the body louse The clinical course is unlike those of the three groups enumerated and the causative micro-organism is much more bacterium like than the others and does not invade the cells of the louse The Weil Felix reaction is negative in Trench fever

Further difficulty in constructing a categorical characterization of rickettsial diseases is presented by the recently recognized (1937) Q disease of Australia and subsequently discovered in this country in Montana and now known to be fairly widely distributed Q fever first known in Montana as Nine Mile fever is not accompanied by a rash it is self limited does not give a Weil Felix reaction and the important lesion in man is a pneumonitis The pathology in guinea pigs is also unlike that of other rickettsial diseases because of the presence of exudative and suppurative processes and minute proliferative lesions widespread in many organs The cause is a rickettsia like micro-organism transmitted by several species of ticks This organism *Rickettsia burneti* (or *Rickettsia diaporia*) has forms which unlike other rickettsiae pass through Berkfeld N filters In infected animals and in tissue cultures the organism grows both intracellularly and extracellularly There is also evidence that Q fever may be transmitted from man to man without the agency of ticks

There is but one proved rickettsial disease of animals—heartwater disease of cattle sheep and goats The organism *Rickettsia ruminantium* is tick transmitted In animals it is found in endothelial cells of blood vessels particularly in brain and kidneys The rickettsiae persist in endothelial cells after recovery of the animal

The Typhus Group—Two types are generally recognized one the classic epidemic European type the other the murine type so called because of its natural reservoir in rats Murine typhus is endemic throughout the world it is transmitted from rat to man by fleas

The Rocky Mountain Spotted Fever Group—No distinction should be made between the disease as it occurs in the South and East of the United States and that of the northwestern states The group includes the tick transmitted so-called *Sao Paulo typhus of Brazil* and other South American countries the *fièvre boutonneuse* of the Mediterranean countries *South African tick bite fever* and *Kenya fever*

Fievre boutonneuse and South African tick bite fever are characterized in this group by local sores (at the site of feeding of the tick) and regional adenitis

In the tsutsugamushi disease group are included the classic *tsutsugamushi disease of Japan rural typhus of Malaya* and the *mite fever of Sumatra* In Japan transmission is by larvae of *Trombicula akamushi* in Malaya and Sumatra also by the larvae of *Trombicula deliensis* and *T schuffneri*

The rickettsiae responsible for these three groups can be distinguished by their morphology and behavior in animals and tissue cultures The rickettsia of the Rocky Mountain spotted fever group *Dermacentroxenus rickettsi* has the unique property of invading nuclei of cells of the tick of susceptible animals and in tissue cultures

children In the latter group nausea and vomiting are very frequently initial symptoms while severe diarrhea with distention may be more striking than the pain Mild sore throat or slight conjunctivitis occasionally occurs Herpes labialis, hiccup and epistaxis are rare A localized pleural friction rub is very rarely heard during the early stages of the disease but no signs of actual pulmonary disease have ever been noted X ray examinations of the chest in the hands of many observers have failed to show any significant abnormalities

Blood cultures have been uniformly negative Bacteriologic examinations of the nasopharyngeal secretions as well as inoculation experiments on animals have yielded negative results The course of the leukocytic count is extremely irregular showing a variation from 3000 to 21,000 In the majority of cases, it is within normal limits A moderate eosinophilia (5 to 13 per cent) is frequently seen during convalescence and particularly in those cases with complicating pleuritis The urine shows only the characteristics common to any febrile condition

Complications —The complications are rather frequent though seldom serious *Fibrinous pleuritis* is the most common occurring in more than 50 per cent in some epidemics Localized friction may rarely be heard during the first day or two but complicating pleuritis does not appear until the end of the first week or even later The friction sound is commonly very loud heard over an extensive area occasionally bilateral, and may persist for weeks The patient can usually feel the rub but is without pain Fluid never develops and the fever disappears after the first two or three days *Fibrinous pericarditis* is a less frequent complication and apparently quite as innocuous *Orchitis* is common in some epidemics *Bronchopneumonia otitis media, pyelitis sinusitis* and *catarrhal jaundice* are among the more unusual complications The principal effect of such complications is to prolong the convalescence as ultimate recovery is complete

Diagnosis —When the disease occurs in epidemic form the diagnosis is seldom difficult as the sudden appearance of the triad, fever, headache and diaphragmatic pain combines to form a picture which is unique The chief difficulty arises in cases with very marked abdominal pain, spasm and tenderness which always suggest the possibility of some local *surgical emergency* If to the above are added nausea vomiting, and distention, as so often happens in children, the picture is still more suggestive The white blood count does not always aid us as we may occasionally find a considerable leukocytosis in epidemic pleurodynia The tenderness in this condition is superficial with unmistakable hyperalgesia of the skin as contrasted with the marked sensitiveness to deep pressure when visceral involvement is present The clinical picture in *dengue* and pleurodynia may show a striking resemblance but the pain localized in the back and joints glandular enlargement and skin rash of the former are usually sufficient to differentiate them *Grippe and influenza* occur in the cold months and the unique type of pain in pleurodynia is never simulated in either

Prognosis —The danger to life is insignificant as among many thousands of cases only 13 deaths are recorded Except for a somewhat protracted convalescence in occasional cases recovery is prompt and complete

Treatment —The course of the disease is so brief that therapy does not play an important role The intensity of the pain indicates the early and liberal use of analgesics such as the salicylates and opiates A swathe to the lower thorax usually furnishes considerable relief from the pain as does the local application of heat Counterirritants at the seat of pain are contraindicated Absolute rest in bed should be enforced as the pain is more easily controlled thereby and the course of the disease probably shortened

EDWIN A LOCKE

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universities and in the Federal Services have set the pattern for research that has uncovered the existence of rickettsial diseases throughout the world Wherever man rodents and ectoparasites common to both exist rickettsial diseases are to be found Their importance economically and as a menace to life is probably exceeded only by malaria The epidemiology of these diseases and preventive measures are to be approached through knowledge of the animal reservoirs and biology of the arthropod vectors

S Burt Wolbach

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TYPHUS FEVER

(*War Fever Ship Fever Jail Fever Prison Fever Camp Fever Hospital Fever Tabardillo Brill s Disease*)

Definition—Typhus fever is an acute infectious disease transmitted sporadically by the rat flea in epidemics by the body louse characterized clinically by sudden onset continuous high fever terminating by rapid lysis after about fourteen days a general macular eruption tending to become hemorrhagic over trunk and limbs but avoiding the face a delirium which may pass into a final coma and a tracheobronchitis often followed by bronchopneumonia Pathologically it is characterized by proliferative and thrombotic lesions of the blood vessels of the skin musculature and central nervous system Epidemiologically there are two types of typhus one of the classic European type exemplified by louse borne epidemics throughout the world the other the murine type with the natural reservoirs in rats and therefore endemic in every country Zinsser has presented evidence that sporadic typhus (Brill s disease) in the United States represents a recurrence of typhus previously experienced in Europe The murine type prevalent in the southern United States is transmitted to man by the flea *Xenopsylla cheopis* possibly also by ingestion of food recently soiled by the excreta of rats The typhus of Mexico (tabardillo), a louse borne epidemic disease is of the murine type Elsewhere in the world the murine type has not been reported in epidemic form

History and Distribution.—Since its recognition as a disease entity in the sixteenth century typhus has been known as one of the great epidemic diseases of the world It has been associated in history with a massing of persons in cities prisons ships and armies and fatal epidemics have attended most of the great wars

Regions which are known to be important centers for the origin of epidemics (European type) are Central Europe Russia Ireland Italy Spain Turkey Abyssinia and Northern China The establishment of epidemics requires a population contented with or forced by circumstances into a state of lousiness

Murine typhus is known to exist in Africa Chile China Greece Indo China Malaya Manchuria Peru the Philippines and the United States It can be the origin of epidemics because after transmission to man by the flea it is carried by the body louse

Endemic Typhus in the United States—Knowledge of murine typhus began with Maxcy s discovery in 1926 that typhus existed in the southern United States unassociated with lice Dyer Rumreich and Badger in 1931 discovered the virus in Baltimore rats and in the same year Mooser Castaneda and Zinsser found the virus of tabardillo in Mexican rats Maxcy predicted that the rat flea would prove to be the carrier to man and this was verified by Dyer and his associates Rodents other than the rat known to harbor the virus of murine typhus are mice domestic and wild squirrels gophers the opossum and the wood chuck

Endemic murine typhus is present in

Immunology—The three groups are distinct immunologically All are pathogenic for many mammals and all have animal reservoirs The rat is the important reservoir for murine typhus and man the reservoir for the European strain Many animals including all rodents, are susceptible to typhus and in some rodents as in rats and squirrels, the infection persists for many months Likewise, most mammals are susceptible to the Rocky Mountain spotted fever group, rodents undoubtedly are of greatest importance in maintaining the virus in nature throughout the world while many species of ticks act as vectors

The one proved Japanese reservoir of tsutsugamushi disease is a field mouse (*vole*) while both house rats and field rats are reservoirs for the Malayan and Sumatran diseases

Rickettsia prowazeki the cause of typhus is pathogenic for the louse in that it fills the epithelial cells of the stomach so completely as to destroy function It is not transmitted through the egg to succeeding generations of lice *Dermacentroxenus rickettsi* even though it invades all tissues of ticks apparently causes no ill effects and is transmitted to succeeding generations via ova and spermatozoa All stages of the tick larva nymph and adult are capable of transmitting *D rickettsi* *Rickettsia tsutsugamushi* (*R orientalis*) has not been studied adequately in its vectors the larvae of *Trombicula* The nymphs and adults of Trombicula feed only upon plants There is some evidence that the rickettsiae are transmitted hereditarily in *Trombicula* although the adult apparently does not contain the virus in infectious form

The pathology of typhus and the Rocky Mountain spotted fever groups has been extensively studied and the nature and distribution of vascular lesions leading to thrombosis and to infiltration and proliferation of cells about small blood vessels explain adequately the oustanding cutaneous and nervous manifestations of the diseases The meagre and inadequate studies of the pathology of tsutsugamushi disease point also to a vascular pathology including minute lesions in the central nervous system

Immunity to typhus and Rocky Mountain spotted fever is of long duration A second and even a third attack have been reported with both but only after lapses of many years According to Zinsser Brill's disease is a recrudescence of European typhus and not a re infection Immunity to tsutsugamushi disease is less complete Re infection is not uncommon but second attacks are usually mild

Prophylaxis—Laboratory attempts to confer passive immunity to the rickettsial diseases in animals have been only partially successful No antiserum satisfactory for the treatment of humans has been achieved No chemotherapeutic agent including sulfanilamide and related compounds has proved to be of value

The voluminous growths of rickettsiae now obtainable by modified tissue culture technics and in developing chick embryos afford some promise of securing more effective immune serums Suspensions of rickettsiae are now also available for the study of specific diagnostic procedures—agglutination and complement fixation reactions—which will probably soon supersede the enigmatic though useful Weil Felix agglutination tests with various OX strains of *Bacillus proteus*

Vaccines for protection against rickettsial diseases consist of chemically killed rickettsiae obtained by various methods Vaccines made from living attenuated viruses are dangerous because in the presence of vectors the virus may be taken up by them and give rise eventually to a fully virulent strain

Notable success in protection against Rocky Mountain spotted fever has been achieved through the use of vaccines made from the tissues of heavily infected ticks Cultures in developing chick embryos are now being employed Typhus vaccines prepared from developing chick embryo cultures from animal tissues and from modified tissue cultures are now under trial and give promise of success The huge armies engaged in the present world war are giving opportunity for the testing of the various types of vaccines

The development of knowledge of the rickettsial diseases since Ricketts began his study of Rocky Mountain spotted fever in 1906 forms a most commendable chapter in American Medicine Investigators in our

examination made by the writer in Warsaw in 1920 small lesions in surprising abundance were present in cerebrum cerebellum medulla and the only portion of the spinal cord examined routinely the upper portion of the cervical cord These lesions are chiefly in the form of small tubercle like lesions proliferative in character composed in large part of neuroglia cells and mononuclear cells of mesenchymal origin macrophages These lesions have been interpreted as being secondary to lesions of small blood vessels and capillaries which are identical in nature with those occurring in the skin The blood vessels of the pia and arachnoid are only occasionally and those of the choroid plexus very rarely, involved In addition to these proliferative lesions which correspond in size to the various dimensions of miliary tubercles there is a *perivascular infiltration* corresponding to that found in many forms of encephalitis The distinctive typhus lesion however is proliferative in character The number and wide distribution of the typhus lesions in the central nervous system may be considered the cause of the severe nervous symptoms which form so prominent a part of the disease

Typhus Fever in Laboratory Animals—In monkeys and guinea pigs typhus runs a definite course as in man The blood vessel lesions are similar and brain lesions are constant In rats the disease is less distinctive and the virus persists for longer periods European typhus produces only an afebrile infection in white rats while endemic or murine strains produce a febrile reaction

Intraperitoneal inoculation of male rats and guinea pigs with the virus of endemic or murine typhus produces a copious exudate abounding in rickettsiae in the tunica vaginalis The European epidemic strains produce in guinea pigs a transient exudate with rickettsiae present at the onset of fever

There is good evidence that strains producing the tunica reaction represent rat flea borne mild typhus and that strains which do not produce this reaction are of a more virulent man louse borne epidemic type Cross immunity between these various strains is complete and cross agglutination of their rickettsiae occurs Recent studies indicate that after louse-man passage the rat flea borne strains acquire characteristics of the European epidemic type On the whole we must conclude that all strains of typhus are identical The tunica reaction to typhus should be distinguished from the scrotal swelling in guinea pigs in Rocky Mountain spotted fever which is caused by thrombosis of blood vessels and occurs irrespective of the manner of inoculation

Symptoms—*Prodromal Stage.*—The period of incubation lasts from eight to twelve days It is probable however that it may be more or less than this because according to the dosage incubation in guinea pigs may vary from five to twenty one days The onset is abrupt although previous to this the patient may recall minor symptoms such as weakness malaise headache while actual elevation of temperature has been observed a few days prior to the true onset

Invasion—As a rule the invasion is abrupt and accompanied by chills or rigor followed by fever from which the patient usually dates his illness Vomiting may occur but is infrequent The appetite may be lost from the beginning but this symptom is not constant The prostration is such that the patient is glad to take to his bed Neuromuscular and back pains are common though less prominent than in influenza and smallpox The fever is high with pulse in proportion and subject to considerable variation from hour to hour The face is usually flushed facies alert or anxious mental condition excited and active delirium may have begun The pulse may be dicrotic the spleen palpable often tender There is no glandular enlargement lacrimation or coryza On the contrary there may be slight dryness of the throat and tongue

Stage of Eruption—Eruption appears on the third to the seventh day usually by the fifth day in the form of round or oval irregular pink erythematous macules which are nonpalpable disappear upon pressure and appear at the base of the neck chest back abdomen and extremities The individual macules are usually 2 to 5 mm in diameter In a few cases the macular eruption is complicated and partially obscured by a mottled erythema which spares the face and is usually most pronounced on the chest back and arms This erythema does not last more than three days and on disap

many southern states Cumming for the six years 1931 to 1936 inclusive has given the number of cases as 300 904 1922 1307 1105, 1662 respectively For the year 1937 the United States Public Health Reports give 2308 cases most of which were distributed as follows Georgia 1006 Alabama 460 Texas 422 Florida 114 South Carolina 81 North Carolina 65

The disease is most common in persons whose occupations bring them into rat infested premises and therefore is most frequent in the handlers of foodstuffs The disease is most common in the late summer and fall The freedom of the population from lice explains the absence of epidemics

Etiology and Transmission —Epidemic typhus is transmitted by the body louse whose fecundity and feeding habits readily explain the rapid passage of the disease from person to person under crowded unsanitary conditions That *Rickettsia prowazeki* is the causative agent of typhus is accepted as proved throughout the world

There is no evidence that typhus is conveyed by sputum or human excreta In the louse *Rickettsia prowazeki* does not invade the salivary glands Because it is discharged in great numbers in the excreta of the louse while feeding it is probable that infection of man takes place through fecal soiling of the punctures or by scratching The virus survives for a number of days in louse excreta (eleven days at room temperature) and it is therefore possible that infection may pass via this medium alone since it has been shown that the virus can enter through slight abrasions of the skin

Epidemic typhus is most prevalent in the winter and early spring and decreases rapidly with the coming of warm weather The increase of clothing with fewer changes in the winter time favors multiplication of lice while the crowding of persons in housing and sleeping quarters facilitates the transference of lice No person becomes heavily louse infected who bathes and changes his underclothing weekly

Endemic (murine) typhus may be carried from rat to rat by the flea *Xenopsylla cheopis* the rat louse *Polyplax spinulosa* and possibly the tropical rat mite *Liponyssus bacoti* From rat to man the probable vector is the rat flea Lice infected with typhus die in about eleven days the rat flea, however remaining alive and infectious for several months

Animals may be infected with murine typhus by feeding materials containing the virus The virus of murine typhus is present in the urine of infected rats and there is reason to believe that humans may be infected by the ingestion of food soiled with rat urine

In endemic typhus in the southeastern United States the peak of incidence occurs in the late summer and fall seasons which correspond to the period of greatest activities of rats and their fleas

Morbid Anatomy —The gross pathology of typhus is not distinctive Many patients die and show but little change at autopsy except the bronchopneumonia often responsible for or contributory to death The *spleen* may be slightly enlarged before the second week, in the third week its size is within normal range The *rash* is usually evident at the time of the autopsy because of its petechial character *Skin necroses* or *gangrene* are occasionally found and there may be symmetrical gangrene of the skin covering the extremities *Thrombi* are rarely found in the large blood vessels The *central nervous system* rarely shows gross changes occasionally there is noted a diffuse pinkish coloration of the cortex with or without minute arachnoidal hemorrhages suggesting the gross findings of encephalitis of whatever origin The pathology of typhus is distinctly microscopical *Proliferative lesions* of the small blood vessels arteries veins and precapillaries are found wherever the rash occurs and in the skeletal muscles The proliferative lesions are usually the site of mural thrombi and occluding thrombi often occur and are responsible for the necroses of the skin seen during life A distinctive perivascular infiltration occurs in the skin producing the so called *typhus nodules* of Frankel In doubtful cases excision of the skin is sometimes resorted to for purposes of microscopic diagnosis Perivascular infiltrations and somewhat similar nodular formation may be found in a few other organs notably the heart while in the *central nervous system* the lesions are perhaps more abundant than anywhere else in the body other than in the skin In every *postmortem*

been noted that in experimental animals the occasional deaths from typhus are those with unusually severe nervous lesions

Clinical Pathology —The *Weil Felix agglutination reaction* is quite constant For this purpose standard cultures of proteus bacillus must be employed Those designated as OX 19 are used and are distributed in laboratories throughout the world Suspensions of living cultures should be used and should be grown upon an agar medium prepared from fresh meat broth accurately adjusted to *p*H 7 4 The medium should be sterilized on three successive days at 100° C Only agar slants with water of condensation should be employed Only the macroscopic technic should be used Readings should be made after incubation at 37° C for two hours and an additional six hours at room temperature In typhus the agglutination reaction does not appear before the fourth day and the highest titer is reached just before or just after the fall in temperature The titer reaches 1 100 to 1 200 by the end of the first week and may at the end of the period of fever reach 1 5000 The initial titer obtained is of minor diagnostic value A rise of agglutination titer during the course of the disease is of great importance as a diagnostic aid

The cultures used for the tests should be constantly checked as the O variant of X 19 is unstable

The *blood* shows no striking changes the white count in uncomplicated cases rarely exceeds 12 000 Cases with marked leukocytosis are unfavorable The *urine* shows changes common to other fevers The *blood pressure* remains strikingly low throughout the disease

Endemic Typhus in the United States — Endemic typhus of murine origin throughout the world is similar in clinical and laboratory aspects to epidemic typhus although it is a much milder disease with a very low death rate

The incubation period is from six to fourteen days The duration of fever is the same as that of epidemic typhus—fourteen days—and terminates by rapid lysis Patients are usually afebrile by the sixteenth day The pulse usually does not exceed 100 The rash is like that of epidemic typhus but is less extensive and petechiae are less frequent Extensive skin necroses have not been reported The pathology in man and in guinea pigs is like that of European epidemic typhus

Complications and Sequelae —*Bronchitis* and *bronchopneumonia* are the outstanding complications of typhus and the chief cause of mortality among the Warsaw cases was bronchopneumonia The onset of pulmonary signs may be insidious or abrupt and it is obvious that various types of infection of the lungs occur chiefly streptococcus and pneumococcus The great irregularity of the heart with rapid and feeble pulse and sometimes evidence of dilatation may be taken as evidence of myocardial degeneration which is often demonstrable at autopsy On the other hand with recovery there are apparently no unfavorable after-effects in individuals who have exhibited marked cardiac signs *Infections of the parotid and submaxillary glands* are not infrequent complications of typhus and should be guarded against by careful cleansing of the mouth *Gastro-intestinal* complications are of minor importance and consist in vomiting and diarrhea The latter is common during the height of the disease The *delirium* and mental disturbance of typhus are to be regarded as a part of the disease rather than as complications *Otitis media* occurs as in other infectious diseases with some frequency *Thrombosis* of large arteries often causes serious complications Peripheral as well as abdominal vessels are affected In the Warsaw series there were cases of thrombosis of the mesenteric carotid pulmonary and splenic arteries Thrombosis of small cutaneous vessels results in the extraordinary necrosis and gangrene of the skin so commonly observed in typhus epidemics Previous impairment of circulation from pressure and cold is suspected as a predisposing cause as the necroses are particularly apt to occur over bony prominences such as the hips sacrum elbows and scapulae The resulting sloughs may involve the underlying subcutaneous tissue and muscles Symmetric gangrene of the extremities also has been frequently noted in typhus

Diagnosis —Prior to the appearance of the rash the signs and symptoms of typhus are so similar to many other *acute infectious*

pearing leaves the macular eruption more clearly evident Rarely large macules are *distinctly palpable The conjunctivae at this* stage of the eruption are markedly injected The tongue in severe cases is dry and per*haps fissured There is usually a cough* which by this time has become loose, and rales sibilant and sonorous are heard over *the lungs The eruption becomes more pro* fuse roughly in proportion to the severity of the disease and in severe cases the lesions *become almost confluent At first light* pink they become deeper pink to bright purplish red, and finally become brownish red in ap*pearance because of extravasation of blood* and on pressure remain a dull red In severe cases more striking purplish red petechiae *occur sometimes of considerable size* Mark

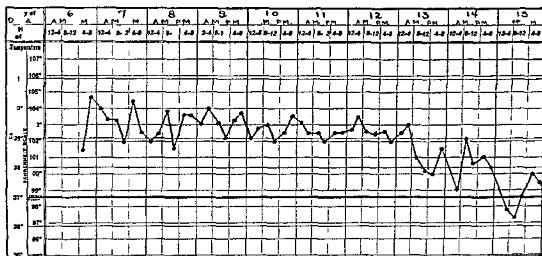


Fig 11—A typical temperature curve of uncomplicated typhus in a young patient who recovered

edly hemorrhagic rashes may be accompanied by hematuria hematemesis and melena and such cases are apt to be rapidly fatal The fever is usually at its height from the fifth to the tenth day More important however, than the fever, in prognosis is the severity of mental symptoms and complications The temperature remains high but somewhat irregular until the tenth or twelfth day when more marked remissions usually appear with a rapid decrease to normal on about the fourteenth day (Fig 11) The pulse rate is *more rapid than in* typhoid and a decrease may precede the fall in temperature The mental and nervous symptoms are *more striking* than in any other acute general febrile disease and in some cases there may be retraction of the head and other symptoms simulating cerebrospinal fever The cerebrospinal fluid however, shows but a slight increase in mononuclear cells and the fluid is not markedly turbid Palfrey attaches great prognostic importance to the mental and nervous symptoms of the patient during the tenth to twelfth days In some cases in spite of a fall of temperature the mental condition becomes worse changing from delirium to coma with carphologia muscular twitchings and incontinence of urine and feces In these cases the rash remains profuse and becomes increasingly hemorrhagic Such patients remain unconscious with increasing exhaustion and emaciation in spite of normal or almost normal temperature for a period of *a few days to a week and die usually with* terminal bronchopneumonia In favorable cases around the tenth or twelfth day a striking improvement occurs Although still delirious the patient becomes quieter, with an appearance of relaxation in spite of exhaustion The flush of the face disappears the pulse is less intense the rash less evident and the skin may be moist The fever becomes remittent and unless complications ensue the *temperature drops to normal* within a few days

The study of the Warsaw cases would *indicate that relatively* mild typhus infections may result fatally because of the severity of the complicating bronchopneumonia while on the other hand severe typhus results in death because of the extensive involvement of the central nervous system It has also

Prophylaxis—Prophylactic measures in general may be summed up as those directed against lousiness Persons attending patients should wear protective clothing preferably a one piece gown constructed with stocking footed trousers with no orifices except at the neck and wrists Close fitting rubber gloves should be worn over the wrists and the neck opening should be sprayed daily with an effective repellent, such as oil of cedarwood or a solution of naphthalene Nurses should wear in addition a head covering to confine the hair The gown should be inspected frequently while being worn and after each exposure should be deloused by heat naphthalene or chloro form Heat is preferable—a temperature of 55° C (131° F) for fifteen minutes is suf ficient Bacot recommends the melting point of stearin about 60° C, as an indi cator If steam is used the temperature should be kept at 65° C or above For bun dles of clothes two to three hours at 100° C is the minimum Bedding or clothing may be disinfected by immersion in hot water at 65° C for thirty minutes or by soaking without heat in 2.5 per cent Lysol for twenty minutes if dried without rinsing Crude flaked naphthalene in a reasonably air tight receptacle kills lice within ten or twelve hours As soon as typhus is suspected the patient should be freed from lice and nits and placed in a louse free environment His previous surroundings should be deloused and quarantined In times of typhus epid emics it is wise to take precautions to pre- vent carriage of lice into the wards by ambulance drivers and other attendants All blankets and clothing removed from the patient should be carried to a disinfecting chamber The delousing of the patient should be superintended by an intelligent and trustworthy person The patient should be clipped with especial reference to head axillae pubic and anal regions bathed thor oughly dried and then sprayed or rubbed with a light oil such as kerosene or liquid petrolatum The head should be generously soused with this oil and tied up in a cloth for twelve hours During epidemics segre gation and quarantine of contacts and im migrants from other typhus infected areas should be required for a period of sixteen days in addition to delousing procedures The methods employed by Strong in the Serbian epidemic were effective There is good evidence from many parts of the world of the value of prophylactic vaccination in times of epidemics The various forms of vaccine prepared from chemically killed sus- pensions of *Rickettsia prowazeki* all appear to be effective in reducing the severity and incidence of the disease

Treatment—There is no specific treat ment for typhus Treatment should be di rected toward supporting the patient and eliminating as far as possible the sources of exhaustion until spontaneous recovery can occur Continuous rest in bed and nursing are most essential An abundant diet of soft solids should be given according to appetite and digestion Liquids should be given fre quently and in abundance Every effort should be made to combat the dryness of the mouth and to keep the oral cavity clean it is advisable to apply a cleansing solution every few hours Where necessary in delirious or comatose patients nasal or esophageal tube feeding should be resorted to Bathing should be practiced as in typhoid The bowels should be kept open with enemas and retention of urine should be guarded against Headache should be treated with an ice bag Antipyretics are to be permitted only when the headache is out of proportion to the severity of the gen eral condition For the exhausting insomnia veronal or chloral and for the more violent delirium hyoscine hypodermically, with or without morphine should be given with the idea of conserving the strength of the pa tient The cough if exhausting should be treated by the usual cough mixtures with the addition of sedatives The onset of pneumonia requires additional efforts to ward diminishing the exhausting effects of restlessness excitement and cough Small hypodermic doses of morphine proved useful in Warsaw The possibility of skin necroses and gangrene should be kept in mind The employment of pads to avoid pressure from bed clothing and frequent changes of posi tion should be instituted upon the slightest indication of these complications There should be constant supervision of typhus patients in order to guard against accidents in delirium After recovery the effects of nervous and mental exhaustion may persist

diseases as to make a differential diagnosis impossible, although in the presence of an epidemic the diagnosis may be made upon suspicion The predominance of chill in typhus and of neuromuscular pains and coryza in other acute diseases is of assist ance *Malaria* and *relapsing fever* may be excluded by examination of the blood for the parasites *Pneumonia* may cause con fusion until characteristic pneumonic symp toms appear, such as accelerated respiration, rusty sputum, and the physical signs *Meningitis* should seldom be mistaken, as menin geal symptoms occur only late in typhus Lumbar puncture would eventually establish a diagnosis In *measles* the coryza and lacrimation give a possibility of early distinction *Smallpox* while it may simulate typhus in the first four days reveals itself later by the characteristic rash *Scarlet fever* is distinguished by the character of the rash and other signs in the throat and on the tongue *Typhoid fever* is so different from typhus in its mode of onset that the dif ferential diagnosis is usually not difficult when a clear history can be obtained Blood cultures and Widal reactions may be re sorted to In the absence of history and in a late stage of the disease there are some differences pointed out by Palfrey The typhus patient is more apt to be excited with active delirium and tense facies in con trast to the more stuporous mental condition and relaxed facies of typhoid The typhoid patient also lacks the injected conjunctivae and shows less flushing of the face The rash in typhus is more profuse than in typhoid and in the latter disease the rose spots are usually palpable and do not become hemor rhagic Skin excision may be resorted to The enlarged spleen persists in typhoid In recent years it has become necessary to dif ferentiate *encephalitis lethargica* in countries where it coexists with typhus The onset is usually gradual as contrasted with typhus the temperature lower rarely exceeding 102° F and the period of fever short There is no splenic enlargement and no eruption In the United States especially in the southeastern section, differential diagnosis between typhus and mild strains of spotted fever may present great difficulties The history of an insect bite or of the crushing of an insect by the patient may be of great importance since spotted fever is carried by ticks, and typhus by the rat flea and body louse (practically always the rat flea in the United States) Louse-borne typhus is most prevalent in the winter flea borne typhus in the late summer and fall and spotted fever in the spring and summer Spotted fever is more apt to produce symptoms in children than typhus and its occur rence is largely in rural districts, while typhus is primarily urban The distribution of the rash differs in the two diseases (see above and below)

The Weil Felix reaction is positive in both diseases Although there are some differ ences in the agglutination reactions to the three strains (OX 19 OX 2 and OXK) of *B proteus* employed they are not suf ficiently constant for the purposes of differ ential diagnosis In many instances it may be necessary to resort to animal inoculation rats and guinea pigs, and to make cross immunity tests

A specific complement fixation reaction for endemic typhus by use of an antigen prepared from rickettsiae grown in the yolk sac of developing chick embryos has been reported by Bengtson and Topping Con sult the chapter on Rocky Mountain spotted fever for a further discussion of the dif ferential diagnosis of typhus and spotted fever

Prognosis —The mortality of typhus in different epidemics has varied greatly 50 and even 70 per cent for one extreme down to approximately 5 per cent for the other In endemic typhus of the United States, according to Dyer, the mortality rate is less than 1 per cent and most of the deaths occur in patients above fifty years of age Factors such as ventilation lack of attend ance food and water and even of beds have undoubtedly contributed to the high mor tality of the worst epidemics There is a general feeling among the laity and phys icians that the educated classes have a higher mortality In childhood the disease is mild, in the second decade it is more severe but death rarely occurs in individuals under twenty years of age The mortality increases with the age The liability to a severe bron chopneumonia becomes greater and also persistent cerebral symptoms play a more important part

cajennense In the mountain states where rabbits constitute a reservoir of the virus the rabbit tick *Haemaphysalis leporis palustris* is the vector among these animals In South America, *Amblyomma cajennense* is the common vector but other ticks are in volved The list of proved and potential vectors of Rocky Mountain spotted fever includes ten species of ticks distributed in four genera

The late recognition of Rocky Mountain spotted fever in the East should not be re garded as evidence of its spread from the West There is reason to believe that the dis ease has existed in some Eastern states for an indefinite period Mild and severe infec tions both occur in all localities and there are no essential differences in the pathology of fatal cases from East and West

The total number of cases reported for the five years 1933 to 1937 inclusive was 2190 with 420 deaths of these 1435 cases and 273 deaths were from the Mountain and Pacific states with a death rate of 19 4 per cent

The mortality varies greatly but remains fairly constant in different localities In the Bitter Root Valley it is over 80 per cent for adults and about 37.5 per cent for children Regions of high mortality exist in other states When the disease was more prevalent in Idaho the mortality was less than 5 per cent now with fewer cases it has increased to above 25 per cent In Brazil the mortality rate is about 80 per cent

Etiology —*Dermacentroxenus rickettsi* the proved cause of the Rocky Mountain spotted fever group has a number of char acteristics which distinguish it from the rickettsiae of the typhus and tsutsugamushi groups in addition to immunological dif ferences Chief of these are its cyclic mor phology in ticks its hereditary transmission in ticks and its intranuclear growth in tick and mammalian tissues

Morbid Anatomy —The study of Rocky Mountain spotted fever has been greatly facilitated by the fact that the disease is exactly duplicated in laboratory animals (monkeys rabbits and guinea pigs) in re spect to its general course and the distribu tion and character of the lesions The pathology of the disease resembles in many respects that of typhus The distinctive gross lesions are those resulting from the thrombosis of blood vessels In the male there is frequently extensive hemorrhage and necrosis in the tissues of the scrotum There also may be necrosis of the skin of the ears face, fingers toes and vulva The spleen in man and animals is enlarged to several times the normal size it is firm and dark red Gross changes in the other organs of the body are essentially lacking The blood is dark red and clots slowly The right side of the heart is commonly dilated but the myocardium shows no change The lungs are normal unless there has been sec ondary pneumonia The gastro intestinal tract pancreas liver the adrenal glands and kidneys show no gross lesions In spite of the hemorrhagic lesions of the testes and ovaries the bladder prostate and uterus show no lesions In cases of long duration the marrow of the long bones becomes red because of resumption of activity The blood vessel lesions consist at first of a prolifera tive reaction of the endothelium followed by thrombosis either mural or occluding A considerable degree of perivascular infiltra tion occurs but the perivascular nodules so distinctive of typhus do not develop The parasite of the disease is found in endothe lial cells and also in smooth muscle cells of blood vessel walls Arteries veins and capil laries are affected Minute focal lesions of the central nervous system resembling those of typhus but accompanied by more con spicuous infarction of arterioles are common in cases which survive more than twelve days and therefore have been most often found in postmortems upon eastern cases Enlargement of the spleen is less marked and hemorrhagic lesions of the skin serous membranes and elsewhere are less common than with the western type

The *clinical laboratory findings* are not impressive The *urine* is that of any febrile disease In uncomplicated cases there is a slight leukocytosis There is an increase in the large mononuclear leukocytes exclusive of lymphocytes The *red cells* decrease in number as the disease progresses and may fall below 3 500 000 Eosinophils are de creased and may be entirely ab ent

The Weil Felix reaction is of some value in diagnosis All three types of *B proteus* employed (OX 19 OX 2 and OXK strains)

for some time and should be taken into account before the patient is permitted to resume normal activities

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ROCKY MOUNTAIN SPOTTED FEVER

(Black Fever Blue Disease Tick Fever)

Definition—Rocky Mountain spotted fever is an acute specific infectious endangiitis, chiefly of the peripheral blood vessels transmitted by ticks and characterized by onset with chills, continued fever terminating in lysis severe pains in bones and muscles headache, and a macular eruption becoming petechial which appears first on wrists ankles and back and then over the whole surface of the body

History—The disease has probably existed in Idaho and Montana since the first settlement by white man and seems to have been known to the Indians before that time It was first described by Surgeon Major W W Wood in 1896 in a report to the Surgeon-General Maxcy of Idaho and McCullough, of Montana gave the earliest clinical descriptions of the disease Important laboratory and field investigations were made by Wilson and Chowning and Ricketts and his associates Ricketts established the transmission of the disease by the tick, and defined most of the problems which have resulted in our present knowledge of the disease and its causation

Distribution, Transmission and Incidence—The generalization may be made that diseases of the *Rocky Mountain* spotted fever group exist throughout the world wherever *Ixodidae* have opportunity to feed upon men Probably most of the rodents and other mammals which nurture the ticks are reservoirs of the rickettsiae In addition, the rickettsiae are transmitted hereditarily in the tick

In the United States the distribution of *Rocky Mountain spotted fever supports* the above generalization The distribution of the disease as known in 1920 included the states of Idaho Montana Utah, Wyoming Nevada Oregon Washington, Colorado California New Mexico, South Dakota and North Dakota The identification of the disease in the East by Badger Dyer and Rumreich in 1931 was followed by the rapid recognition of its prevalence in the Central and Eastern States Now, July 1942 the only states from which the disease has not been reported are Maine Michigan, Mississippi New Hampshire, Vermont and Wisconsin In the East the highest incidence is in Maryland Virginia and North Carolina

In the Rocky Mountain Pacific coast states the wood tick *Dermacentor andersoni* is responsible for transmission to man In the East and South the dog tick *Dermacentor variabilis* is the important carrier The brown dog tick *Rhipicephalus sanguineus* of the South and East, is probably also a carrier to man as laboratory experiments indicate and because it is the known transmitter of fievre boutonneuse

The seasonal incidence of spotted fever corresponds to the tick seasons of the locality concerned In the northwestern region *Dermacentor andersoni* appears in February and a few can be found during August and September They are most prevalent from the middle of March to the middle of June and hence spotted fever in that region occurs from March to July, with occasional cases later up to October

Dermacentor variabilis in the East appear in March and are most abundant from May to July though found as late as November and December Eastern spotted fever has been reported from March to December with the greatest incidence in June and July

Other ticks of the United States which may transmit the disease because they feed upon man are *Dermacentor occidentalis* *Amblyomma americanum* and *Amblyomma*

is due to stasis of blood in the subcutaneous vessels because of thrombosis In mild cases the rash does not become confluent and the petechiae, remaining small give a peculiar mottling which several Idaho physicians have compared to the markings of turkeys eggs Slight icterus may appear in the second week of the disease The rash begins to disappear with the subsidence of fever, but may long be indicated by the persistence of pigmented spots *Necrosis* of the skin of the scrotum prepuce fingers toes vulva lobes of the ear, and mucous membrane of the soft palate may occur in the third week *Desquamation* follows recovery but is slight except where the lesions have been most marked Minute cicatrices in the skin may persist for a long time after recovery

Nervous Symptoms—Restlessness and insomnia are very common through the disease and constitute its most distressing features Hyperesthesia may be severe Delirium is usual in severe cases during the height of the fever and coma usually precedes death by a few hours or a day Rarely convulsions muscular rigidity and opisthotonos occur Following recovery deafness visual disturbances slurring speech and mental confusion for a few weeks have been noted

Complications—Pneumonia is the one complication and is not frequent

Immunity—Recovery from Rocky Mountain spotted fever is accompanied by complete immunity for a long period of years According to Parker (1938) second infections have been reported eight or more years after the first in some instances ending fatally In guinea pigs recovering from feebly virulent strains does not protect fully from highly virulent strains Recovery from virulent strains does confer complete and lasting immunity in animals

A brief period of passive immunity may be conferred by the injection of blood from an immune animal

Active immunity can be produced by the injection of chemically killed rickettsiae obtained either from emulsions of the organs of infected ticks or from tissue cultures

The vaccine prepared from ticks by the United States Public Health Service which has been used since 1925 is of proved value in prophylaxis Its use has reduced the number of cases It protects completely against less virulent strains and greatly ameliorates the severity of the disease in regions of greatest virulence As the immunity reaches its height within a year, the vaccine should be used each spring in order to protect persons constantly exposed to the disease

Diagnosis—Theoretically the same diseases must be considered in the differential diagnosis of Rocky Mountain spotted fever as in typhus but practically the seasonal incidence and restricted distribution of the disease eliminate a number of possibilities *Cerebrospinal fever* and *measles* are the two diseases most liable to be temporarily mistaken for Rocky Mountain spotted fever In cases of doubt spinal puncture should be resorted to when there is a question of cerebrospinal fever as the rash may simulate that of Rocky Mountain spotted fever Usually the more severe nervous symptoms with early rigidity of the neck and character of the onset should serve to differentiate the two Measles at its height in children presents difficulty as the rash may resemble the early rash of spotted fever very closely The history of slower onset with coryza and lacrimation the presence of Koplik s spots the absence of severe muscular pains and the papular character and sequence of distribution of the rash are the most important differential data Typhoid fever with a pronounced rash may also have to be excluded The rash in typhoid fever however is more palpable and elevated than in Rocky Mountain spotted fever and is generally more restricted to the trunk A slower pulse rate lower fever diarrhea and positive blood cultures, or a positive Widal make final exclusion easy

Since Rocky Mountain spotted fever and endemic (murine) typhus co exist in at least twenty three states the problem of differential diagnosis often arises

Spotted fever is essentially a rural disease and exposure to ticks is important Most cases occur in the spring and early summer Endemic typhus is essentially urban it is a disease of late summer and autumn and occurs most often in persons frequenting rat infested premises and hence in those handling foodstuffs

The outstanding clin cal difference is in the evolution and distribution of the rash

may be agglutinated but most often the OX 19 strain is agglutinated in highest titer occasionally the OX 2 titer is higher and rarely the OXK strain gives the highest titer A titer of 1 320 is the lowest that can be considered diagnostic, but as in typhus a rising titer during the course of the dis ease is of greatest significance A test should be made as early as possible in the disease and repeated after the tenth day A signif icant reaction may not be obtained until convalescence has begun

A differential diagnosis between Rocky Mountain spotted fever and the other rick ettsial diseases should not be attempted by means of the Weil Felix reaction *

Symptoms —*Incubation* —The incuba tion period in the more severe infections is two to five days and in the milder ones from three to fourteen days

Prodromal Stage —Before the definite on set of the disease there may be a few days of malaise accompanied by chilly sensations and loss of appetite The prodromal stage is more common in Idaho where the disease is less severe than in Montana The *onset* is usually accompanied by a chill and there are severe general pains referred to the bones muscles back and joints, particularly in the calf muscles large joints and lumbar region of the back Headache is common and severe The face is flushed the conjunc tivae injected and the tongue white coated with moist edges and tip Constipation is usual There is usually photophobia and there may be epistaxis A short dry cough is common The patient is frequently ill enough to take to bed on the second day of symptoms

TEMPERATURE —Before the initial chill there may be slight evening elevation of temperature Following the chill the tem perature rises fairly rapidly and reaches 102° to 104° F (38 8°–40° C) by the sec ond day It continues to rise gradually to a maximum of 104° to 105° F (40°–40.5° C) during the second week In very severe cases in the Bitter Root Valley temperatures from 106° to 107° F have been recorded The maximum temperature persists during the second week of the disease, with slight morning drops With recovery the tempera ture begins to fall at about the end of the second week, continuing by lysis, so that normal temperature is reached at about the end of the third week After recovery the temperature may be slightly subnormal for a few days In fatal cases the tempera ture may drop to normal or subnormal and then rise eighteen to twenty four hours be fore death which in severe cases usually takes place between the sixth and twelfth days of the disease

The PULSE is at first full and strong but gradually loses volume and strength, and increases in rapidity out of proportion to the fever The pulse rate ranges from 110 to 140 and may reach 150 a few days before death A pulse rate of 120 with a tempera ture of 102° F is not uncommon

The RESPIRATIONS behave very much as does the pulse They are rapid and out of proportion to the apparent severity of the illness usually 30 to 40 a minute but in creasing occasionally to 60 before death

The RASH appears usually on the third fourth or fifth day of fever most often on the third, occasionally as early as the sec ond or as late as the seventh day It appears first on the wrists ankles and back then on the forehead, arms, legs chest, and abdomen The efflorescence requires twenty four to thirty six hours although the eruption may appear still later than this on the palms of the hands, soles of the feet, and scalp The mucosa of the cheeks palate fauces and pharynx may show the eruption The tem perature is not appreciably affected at the time of the eruption but the subjective symptoms ameliorate The rash at first is in the form of rose colored macules 1 to 4 or 5 mm in diameter not elevated not pal pable and disappearing upon pressure The skin may be tender at the site of the spots The macules soon become deep red or purplish in color and increase in size often becoming confluent After a few days the rash begins to persist upon pressure and then becomes generally petechial in char acter Cutaneous and subcutaneous hemor rhages of considerable size occur frequently in severe cases and the skin in the second week of the disease may assume a glazed appearance Where the skin is thin as over the thighs a peculiar dusky reddish or bluish mottling may often be seen which

* See Typhus Fever for further considerations of the Weil Felix reaction

ing may be employed to reduce temperature in the absence of hyperesthesia Antipyretic drugs should be avoided Hypnotics such as morphine codeine and hyoscine may be recommended when the hyperesthesia restlessness and insomnia become of importance in the production of exhaustion All efforts should be directed toward keeping up the strength of the patient and hence the diet should be nutritious liberal and easily digestible particularly during the first stages of the disease Liquids should be given in abundance and a daily movement of the bowels secured by enemata or aperients Digitalis may probably be used to advantage as in pneumonia a few doses should be given at the onset of the disease in order to digitalize the heart and should be followed by others when the pulse rate becomes unduly high On theoretical grounds the transfusion of blood from an immune donor should be tried when opportunity occurs in the early stages of the disease

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TRENCH FEVER

(*Quintan Fever Shin Bone Fever Wolhynian Fever His Werner Disease etc*)

Definition—Trench fever is a specific exanthematic louse borne infection characterized usually by a sudden febrile onset with pain and soreness in muscles bones and joints and by a tendency to relapse weeks or months after the primary attack The disease is remarkably protean in its clinical manifestations but is never fatal

History—The disease was first recognized in 1915 when it appeared on the western and eastern fronts during the World War possibly imported from an endemic focus in Russia. Evidence of its occurrence in previous wars is difficult to evaluate It constituted one of the major medical problems of the war because of the tremendous amount of disability which it caused, and was investigated intensively by a British and by an American commission Following demobilization the disease practically disappeared but presumably retains the potentiality of again becoming epidemic if similar conditions of overcrowding and lousiness should ever be reproduced A recent report (1941) of a small outbreak of trench fever among laboratory workers on whom supposedly normal lice were being fed in the process of making typhus vaccine suggests that a reservoir of the disease may still exist in lice

Epidemiology and Etiology—The responsibility of the body louse in transmitting the disease to man was established by both British and American commissions as a result of well controlled louse feeding experiments upon human volunteers The virus is present in the excreta of lice where it may remain infective for several months In the human patient during the active stage of the disease it is constantly present in the blood often in the urine and occasionally in the saliva and sputum The disease is transferable from man to man by intravenous inoculation of blood but not by rubbing blood into the broken skin

Experimental transfer of the infection from louse to man was much more readily effected by rubbing louse feces into the scarified skin than by merely allowing lice to feed upon human subjects Practically all virus free control lice became infective about nine days after feeding on febrile patients and in some instances infectivity appeared in lice fed upon apparently recovered patients ten or twelve weeks after subsidence of signs and symptoms

Regarding the nature of the etiologic agent there is strong but perhaps not conclusive evidence incriminating an organism (*Rickettsia wolhynica R pediculi R quintana*) the presence of which in the intestines and feces of lice was definitely correlated with infectivity by Bacot Arkwright and Duncan The principal difficulty in accepting this organism was its occasional occurrence (on the continent but not in England)

In endemic typhus it appears first on the chest and upper abdomen and usually spares the palms and soles and rarely involves the face and neck wrists and ankles

Animal inoculations and cross immunity tests may be necessary to decide which disease is encountered Male guinea pigs and male white rats should be used If possible at least 4 cc of whole blood should be injected intraperitoneally into each of several rats and guinea pigs A heavy exudate with an abundance of rickettsiae in the scrotal sac of either animal is strong evidence of endemic typhus if in the rat the evidence is conclusive If the animals react mildly, a final opinion can be given only after cross immunity tests following their recovery Serum from a convalescent patient with doubtful diagnosis may be tested in guinea pigs for protective value against the viruses of typhus and Rocky Mountain spotted fever in laboratories where these strains are at hand

Recently a specific complement fixation test using suspensions of cultivated rickettsiae for antigen has been devised

Prognosis—The severity of the rash in Rocky Mountain spotted fever is without prognostic importance Patients with severe nervous symptoms are to be regarded as gravely affected The critical period in the disease is toward the end of the second week and the pulse and respiration rates furnish the best guide in regard to the severity of the case A sudden increase in the white count as indicative of a secondary infection, usually means a fatal termination The mortality rates in various regions have been given above In all regions the disease is much more fatal in adults than in children and is most fatal in the aged

Prophylaxis—The general measures to control the disease are directed toward the reduction of numbers and the limitation of distribution of ticks The two methods of greatest practicability and which have met with some success in the Bitter Root Valley are the destruction of the small mammals which act as hosts to the larvae and nymphs and the dipping of cattle infested with adult ticks Clearing and cultivation of the land have made regions safe that were formerly unsafe Lands unfit for agriculture promise to remain sources of infection unless the ticks can be controlled by new methods The introduction of a fly (*Ixodiphagus caucurtei*) parasitic upon *Ixodidae* into a restricted region in Massachusetts in 1926 was effective in reducing the number of ticks in the years following Larger scale experiments in the Bitter Root Mountain country have not been encouraging

In some eastern regions a reduction in number of ticks could be effected by reducing the number of several species of wild mice which are host to the immature stages of *Dermacentor variabilis* Poisoned baits as employed by orchardists would seem most practicable Personal prophylaxis means the avoidance of tick bites This is not difficult for the casual traveler but is very difficult for those who work in tick infested regions A protective one piece working costume may be improvised by sewing trousers and shirt together The trousers should be worn inside heavy woolen socks with high laced boots It is also advisable to interpose a strip of greased felt or other absorbent material in the neck band and wrists Stripping and inspecting the body for ticks would greatly diminish the chances of contracting the disease as the tick is slow to attach and ordinarily remains attached for a short period before beginning the act of feeding

Exposed children should be inspected at noon and night When camping the bedding should be carefully inspected morning and night Ticks attached to the body should be removed at once by gently pulling them off with the fingers crushing them should be avoided An effective cauterizing agent like crude phenol should be introduced by means of a sharp pointed bit of wood into the point of attachment after removal of the tick Silver nitrate though less effective is easier to carry

The vaccine of Spencer and Parker has proved to be of definite value and should be given each year to persons liable to be exposed to the disease The immunity it gives lasts only about a year but it is sufficient to prevent or markedly ameliorate the disease A vaccine prepared from the yolk sacs of developing chick embryos (method of Cox) is now under trial

Treatment—There is no specific treatment The measures to be used are those employed in other continued fevers Bath

Pain and soreness in the muscles usually recur with each febrile relapse Lumbar pain is most apt to persist in the chronic stage of the disease Abdominal pain and tenderness probably of muscular origin are usually bilateral and more pronounced on gentle than on firm pressure This fact together with the palpable spleen rash and generalized pain and tenderness usually serves to differentiate the condition from appendicitis

Prognosis —The disease has no mortality Its duration is extraordinarily variable but about 85 per cent of all patients are able to return to work within two months of the time of onset It is believed that in about 5 per cent of all cases the disease becomes chronic necessitating a much longer period of time for complete recovery Recovery is apt to be delayed in the aged and in the *debilitated*

Diagnosis —During epidemics typical cases are readily diagnosed on the basis of the symptomatology outlined above The atypical abortive cases may be confused with influenza in the absence of the characteristic rash The mild character of respiratory symptoms and the enlarged hard spleen of trench fever are valuable differential criteria in such cases The differential diagnosis from appendicitis has already been considered The typhoidal type is differentiated from true typhoid by the negative Widal reaction and by the almost constant presence of mild to moderate leukocytosis rather than leukopenia In typhoid typhus and dengue fever the onset is more gradual than in trench fever and the rash usually appears several days later Spirochetal relapsing fever and *malaria are ruled out best by examination* of the blood for their specific etiologic agents In cases of the chronic type with tachycardia fatigue loss of weight and symptoms of neurasthenia diagnosis may be most difficult It is theoretically possible to establish strong presumptive evidence of trench fever by feeding carefully controlled lice on such patients and finding that they acquire *Rickettsia wolhynica*

Treatment —No well-established or rational specific treatment is available Pain and discomfort should whenever possible be controlled by such drugs as aspirin and phenacetin rather than by opiates Codeine is useful in cases of severe pain Insomnia can usually be controlled by hypnotics The patient should remain in bed under the best available hygienic and dietary conditions for a week or more after complete cessation of subjective and objective evidence of infection He should be kept under observation for several months, and returned to bed at the first sign of relapse Eventually work may be gradually and cautiously resumed

Prophylaxis —Prevention of the disease is largely a question of efficient delousing Destruction of the virus on clothing contaminated by louse excreta is also of primary importance Since the virus has been found to withstand moist heat at 70° C autoclaving is probably the most satisfactory method Disinfection of urine and sputum may be carried out by chemical *methods or by heat* Louse *proof garments* and rubber gloves should be worn by those attending patients or handling clothing Trench fever patients are best treated in separate wards It must be borne in mind that lice may become infected from apparently recovered individuals many months after the disappearance of symptoms

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TSUTSUGAMUSHI DISEASE

(Japanese Flood Fever Kedani Disease Rural Typhus Tropical Typhus—Type K)

Definition —Tsutsugamushi disease is a *specific* mite borne infection characterized by a febrile course of two or three weeks duration a generalized cutaneous eruption

in lice which were not infective This objection could readily be met by assuming that this organism may at times occur in a nonvirulent form

The organism occurs extracellularly in the gut of the louse, thus differing from other pathogenic rickettsiae Since intracellular multiplication is usually regarded as an outstanding characteristic of this rather arbitrary group it is possible that the names assigned to the trench fever organism may eventually be withdrawn For the present however, they have considerable pragmatic value and for this reason should be retained

Important confirmatory evidence of the etiologic role of *R wolhynica* was obtained incidentally through the illness of Mr Bacot while in Warsaw as a member of the Typhus Research Commission in 1919 A strain of lice absolutely free from organisms brought from England as a control for the typhus work was being fed on Mr Bacot at the time when he developed an illness considered typical of trench fever by well qualified clinicians This infection was presumably acquired from local Warsaw lice which were also being fed on Mr Bacot at the time Twenty days after the onset of his illness the rickettsia free control lice being fed on Mr Bacot developed large numbers of *R wolhynica* and he continued to infect this control strain of lice for a period of several months

It seems justifiable on the whole to regard *R wolhynica* as the presumptive cause of trench fever The lack of a susceptible experimental animal makes absolute proof impossible at present

Morbid Anatomy —Postmortem studies have not been made since the disease is never fatal Examinations of excised macules from the skin have apparently shown no important specific changes The spleen is usually enlarged and firm to palpation *Rickettsiae* have not been satisfactorily demonstrated in human tissues

Symptoms —INCUBATION PERIOD —Evidence obtained from the inoculation of volunteers indicates that the usual incubation period is from ten to twenty days with extreme limits of five to thirty eight days depending largely on the dosage employed Prodromal symptoms of headache and general malaise may occur at any time after *the first twenty four hours of the incubation* period

ONSET —The onset is usually acute with chills and a rise in temperature to 102° or 103° F Severe headache usually behind the eyeballs and complete anorexia are almost constant at this stage Nausea and vomiting sometimes occur Laryngitis and bronchitis may be present but are rarely severe Perhaps the most characteristic symptom is severe 'myalgic' pain in various parts of the body, but most prominent in the lumbar region and legs There is also muscular soreness pain in rotating the eyeballs, conjunctivitis and photophobia Occasionally the *onset is insidious and symptoms of* neurasthenia and tachycardia may first call attention to this more chronic form of the disease

Course of the Disease —The progress of the disease is remarkably vagarious The fever and symptoms may last only two or three days or may be typhoidal in character lasting two or three weeks A very common form is that in which there are two febrile periods of three to five days each with twelve to twenty four hours of remission between them Again there may be short febrile periods of only twenty four to thirty hours, recurring regularly every five days for a variable period of time Relapses are prone to occur several weeks or several months after apparent recovery In most cases immunity appears to develop eventually, although relapses have been noted after several years

The characteristic *rash* usually appears during the first twenty four hours and thereafter comes and goes with fever even in the cases of late relapse It is composed of red macules 2 to 10 mm in diameter appearing first on the chest and abdomen and usually confined to those regions although it may involve the entire trunk The extremities are occasionally involved but the face always escapes

The pulse rate during the initial acute attack is increased in proportion to the fever but may be relatively much higher in late relapses A sharp increase in the pulse rate often precedes and may be the only objective evidence of a relapse Tachycardia and dyspnea on exertion are common symptoms in the more chronic form of the disease

protective suits and chemical sprays are obvious methods of prophylaxis Preventive vaccination along the lines developed in typhus and spotted fever is theoretically possible but has not been attempted Immune serum therapy is in the experimental stages in all rickettsial diseases

In general treatment should be symptomatic and supportive the principles being identical with those employed in other rickettsial diseases (typhus and spotted fever) Cauterization of the site of attachment of the vector is probably useless unless done almost immediately after detachment

In experimental animals the sulfonamides cause lowered resistance to typhus and spotted fever and present evidence strongly suggests that these drugs are contraindicated in all rickettsial diseases

HENRY PINKERTON

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CARRION S DISEASE

(*Bartonellosis Oroya Fever Verruga Peruviana*)

Definition —Carrion s disease is a specific arthropod borne infection caused by a minute Rickettsiae like micro organism and characterized clinically by an acute febrile anemic stage (Oroya fever) followed, several weeks later by a nodular cutaneous eruption (verruga peruviana) Either of these stages may be inconspicuous or apparently absent and for this reason the two clinical pictures were originally regarded as separate diseases

Distribution and Epidemiology.—The disease has been found only in narrow valleys in the Andes Mountains at altitudes between 2000 and 9000 feet Until recently it has been largely confined to Peru with a few cases in Ecuador Chile and Bolivia, but in 1939 a serious outbreak was reported in Colombia, suggesting that the distribution may be more widespread than has been supposed The distribution of the disease corresponds in general to the habitat of its probable sandfly vectors *Phlebotomus noguchii* and *P verrucorum* but in Colombia lice and ticks have been suggested as vectors Many natives of the infected areas have asymptomatic infections revealed only by blood culture Severe epidemics in Peru have often been associated with the importation of railroad workers from noninfected regions A reservoir for the infection in lower animals has been suspected but not found

Etiology—The etiologic agent was first seen in the red blood cells in the anemic form of the disease by Barton in 1909 and was named *Bartonella bacilliformis* by Strong *et al* in 1915 It was cultivated in Noguchi s leptospira medium by Noguchi and Battistini in 1926 Noguchi s original evidence of the etiologic identity of Oroya fever and verruga peruviana was further confirmed by new methods of approach by the Harvard 1937 Expedition to Peru and the unity of the two conditions must be considered as established beyond a reasonable doubt

Rats dogs and a number of other mammals suffer from latent bartonella infections which after splenectomy evolve into a severe anemia comparable to Oroya fever Cutaneous lesions apparently do not occur in lower animals Except for the transmission of human bartonella infection to monkeys each species of bartonella appears to be completely specific for the species of animals from which it is recovered

and usually by an ulcerative and necrotic lesion at the site of attachment of the vector with swelling and tenderness of the regional lymph nodes

Distribution —*Originally described in the* flood basins of the large Japanese rivers, the disease is now known to occur also in Formosa, Sumatra the Malay Peninsula, the Bako Islands the East Indies and the Philippines Tropical typhus—type K (rural typhus) is apparently a strain variation of tsutsugamushi It should be borne in mind that statements regarding the distribution of rickettsial diseases have only temporary value During the past twenty years, diseases of this group believed to be sharply restricted to definite areas, have been found to occur often in a slightly modified form and with different insect vectors and intermediate mammalian hosts in regions widely separated from one another Whether this is the result of more careful world wide study of obscure febrile diseases or of migration of infected mammalian hosts has not been determined

Etiology and Epidemiology —Recent work by Japanese investigators has established the rickettsial nature of the disease rendering other theories of historical interest only The disease may be propagated serially in rabbits by the injection of the virus into the testicle where the minute bacterium like intracellular parasite inhabits the interstitial cells or into the anterior chamber of the eye where it develops within the corneal endothelial cells overlying *Descemet s* membrane The etiologic agent has been named *Rickettsia nipponica R orientalis* and *R tsutsugamushi* by different Japanese schools but its relationship to other rickettsiae has not been fully studied and its assignment to a permanent systematic status is perhaps premature

The disease outside of Japan proper occurs in regions which are being cleared for cultivation as well as in river basins The role of the larval form of the mite (*Trombicula akamushi*) in carrying the infection to man and the existence of a rodent (vole) reservoir are two generally accepted facts which make the epidemiologic problems similar to those involved in spotted fever and typhus

Morbid Anatomy —As in other rickettsial diseases there are no distinctive gross lesions in the viscera The local lesion is said to be a coagulation necrosis, probably resulting from endangitis The spleen is en*larged and* there is generalized visceral congestion

Symptoms —The local lesion is a sharply *defined round ulcer several millimeters in* diameter with a black necrotic center and surrounding red areola It usually develops two or three days after the infection by the mite and is *followed in a few days by marked* inflammation of the regional lymph nodes and generalized symptoms (The bite of *Trombicula akamushi* when noninfective produces local inflammation and pain *without* necrosis)

In the early stages of the disease, general malaise headache anorexia insomnia and photopsia are most constantly present Joint pains and epistaxis occur occasionally When the local lesion and lymphadenitis are ab*sent as is often the case in mild epidemics* occurring outside of Japan proper, the febrile reaction develops more rapidly but the course of the disease is shorter and the mortality lower than when these initial signs are present Leukopenia is an almost constant finding in severe cases The rash which is of the maculopapular type is distributed over the entire surface of the body and is not associated with itching or pain Symptoms vary greatly in severity in different local epidemics the mortality ranging from 3 to 60 per cent

Diagnosis —The characteristic local lesion and bubo and the Weil Felix reaction (ag*glutination in moderately high titer* with OX K and negative results with OX 2 and OX 19) are the important features in differentiating the disease from typhus and spotted fever Unfortunately in the mild epidemics occurring outside of Japan proper these criteria are less constant and consequently of less value Low mortality low agglutination titer absent or inconspicuous primary lesion and rash and absence of leukopenia are characteristic of these atypical forms of the disease Animal inoculation crossed immunity tests and other special laboratory studies may be necessary to establish a diagnosis in such cases

Prophylaxis and Treatment—Eradication of the mite and avoidance of its bite by

sionally they are seen in large numbers on the mucous membrane of the mouth and pharynx They are ovoid or spherical in shape and usually half buried in the subcutaneous tissue and covered with thin bluish epidermis which often breaks down leading to ulceration and secondary infection Healing occurs with little or no cicatrization after a period of several weeks The cutaneous stage has no mortality *per se* The possible complications are hemorrhage and local secondary infection neither of which is apt to be serious

Diagnosis —The diagnosis is made from a history of residence in an infected area and on the clinical pictures described above Finding bartonellae in the erythrocytes in blood films establishes the diagnosis in the anemic stage In the cutaneous stage a nodule may be excised and bartonellae may be demonstrated in the endothelial cells Blood cultures in Leptospira medium are positive in both stages Rarely the cutaneous nodules may appear a year or more after an uneventful visit to an infected area Yaws which may simulate verruga peruviana can be differentiated by the demonstration of the specific organism

The blood smear in addition to the infected red cells shows a leukocytosis with a normal differential count except for the presence of numerous myeloblasts The anemia is of the megaloblastic type with a high color index and many megaloblasts normablasts poikilocytes and polychromatophilic cells

Treatment —The treatment of the febrile anemic stage of the disease should be supportive and symptomatic as is any other acute infection Transfusions of whole blood are of undoubted value in severely anemic cases The transfusion of blood from recovered cases has not been demonstrated to be of definite value Arsphenamines which apparently exert a favorable effect on bartonella infection in rats have been disappointing in the human disease and are probably of doubtful value Sulfa drug therapy is not beneficial in rat bartonellosis Liver therapy would seem rational but in practice does not appear to be of value Iron should be given during convalescence The cutaneous stage rarely requires treatment except general cleanliness Excision of necrotic, secondarily infected nodules may occasionally be indicated

Prophylaxis —Since the sandfly does not emerge from the rocky caves in which it lives until after dark it is possible for visitors in the infected areas in Peru to avoid infection by descending below an altitude of 2000 feet or ascending above 9000 feet to spend the night If it is necessary to spend the night in the infected area reasonable security against infection can be obtained by screening The possibility of other insect vectors in Colombia has already been commented on The nature of the country in the Peruvian Andes would scarcely permit a successful attack on the sandfly vector

HENRY PINKERTON

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THE BACTERIAL DISEASES

PNEUMOCOCCAL INFECTIONS

INTRODUCTION

THE pneumococcus is one of the most prevalent of the pathogenic bacteria in the temperate zone It occurs in a comparatively harmless form in the buccal cavity of man and of many animals In such conditions its virulence may be almost nil On the other hand where it acts as the cause of disease it may become one of the most virulent of all the bacteria killing mice in doses as small as one ten millionth cubic centimeter of broth culture The importance of the pneumococcus as a cause of infection is due

Morbid Anatomy—Postmortem studies of fatal cases of the anemic form of the disease show pallor, enlargement of the spleen and lymph nodes and a megaloblastic hyperplasia of the bone marrow The endothelial cells lining small vessels in the lymph nodes, spleen, liver, bone marrow adrenals kidneys and many other organs are greatly swollen and with suitable fixation and staining are seen to be packed with small bacillary and coccoid organism (bartonellae) often occurring in clusters Organisms are also present in the erythrocytes Cutaneous nodules are rarely seen at autopsy, since they commonly do not appear until convalescence from the anemic phase is well established Microscopically the cutaneous nodules have the appearance of rapidly growing capillary hemangiomas Bartonellae may be demonstrated within the endothelial cells with suitable technic Clusters of degenerating bartonellae in the cytoplasm may stain uniformly and resemble inclusion bodies

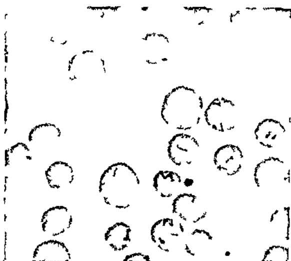


Fig 12—Carrion's disease Giemsa stained blood films showing *Bartonella bacilliformis* in red blood cells Both bacillary and coccoid forms are seen

Symptoms and Course of the Disease—*Anemic Form (Oroya Fever)*—The incubation period is believed to be fourteen to twenty one days In severe cases the onset is sudden, with intermittent fever ranging to 104° F progressive pallor emaciation prostration rapid pulse and dyspnea Muscle and joint pains headache and insomnia are also common symptoms and delirium and coma are apt to be terminal manifestations A petechial cutaneous eruption *occasionally* appears during the febrile period The erythrocyte count may fall from normal to less than 1 000 000 in four or five days, more rapidly than in any other condition exclusive of actual hemorrhage Examination of alcohol fixed Giemsa stained blood films shows bartonellae in the erythrocytes in large numbers, 90 per cent of the red cells frequently containing from one to fifty or more organisms Many reticulocytes and nucleated red cells are present in the blood In the severe form of the disease described above the mortality is 90 to 95 per cent Secondary infection, particularly with paratyphoid bacilli has been emphasized as an important factor in fatal cases, but this view was not substantiated by the author's personal observations The average duration of this anemic stage of the disease is from one to three weeks occasionally the condition of the patient remains critical for a period of eight to ten weeks Convalescence is accompanied by a disappearance of the organisms from the red cells and rapid blood regeneration, but blood cultures may be positive for many months after apparent recovery Reliable evidence indicates that *most if not all of the cases which recover* from this febrile anemic stage develop cutaneous nodules (verrugas) during or even after apparently complete convalescence

Cutaneous Form (Verruga Peruviana)—This form of the disease characterized by cherry red hemangioma like cutaneous nodules may follow the severe anemic form, or may occur in individuals who have had no previous symptoms Intermediate cases are also frequently seen in which there is moderate anemia with rare bartonellae in the red cells slight or no fever and only a few days of malaise *followed weeks or* months later by typical cutaneous eruption The appearance of the cutaneous nodules may be immediately preceded by a few days of moderate fever with joint pains

The cutaneous nodules (verrugas) are commonly 2 to 10 mm in greatest diameter but range up to 3 or 4 cm They may be single or extremely numerous These are most numerous on the head hands feet and lower arms and legs, and are rare on the thighs abdomen or lower chest Occa

growth Furthermore the body fluids and at least some of the tissues of patients with pneumococcal infection contain demonstrable quantities of SSS The amount of SSS appearing in the urine varies with the patient and has considerable prognostic importance

The *virulence* of the pneumococcus can be rapidly increased by repeated passage through animals When freshly isolated from serious infections it usually possesses high virulence but this is gradually lost by growth on culture media In human infections the pneumococcus is prone to be a secondary invader but it can act as a primary infectious agent under certain circumstances In ordinary times about 75 to 80 per cent of all pneumonias are caused by some type of pneumococcus The pneumococcus is therefore primarily the specific agent in the etiology of lobar and lobular pneumonia However the pneumococcus is responsible for a considerable amount of morbidity outside of the lungs The acute respiratory infections of children are often complicated by pneumococcal infections in the middle ear and mastoid Pneumococcus Type III infections in this locality are particularly serious especially when they are complicated by thrombosis of the lateral sinus or brain abscess Pneumococcal meningitis is seen most frequently as a complication of pneumonia but may follow middle ear or sinus infection When secondary to pneumonia pneumococcal bacteremia is responsible for the secondary invasion of the meninges Pneumococcus meningitis was formerly fatal in almost 100 per cent of cases but the introduction of sulfonamide therapy has changed the picture somewhat An increasing number of cases have been cured when treated early with sulfathiazole or sulfadiazine by the oral or intravenous route This is particularly true of those cases which are secondary to mastoiditis Acute pneumococcal infection of the accessory sinuses is a frequent complication of the common cold Pneumococcal bacteremia of cryptogenic origin is encountered usually in children It is conceivable that in these cases the pneumococcus enters the body through the lungs without inducing a local lesion It is much more probable however that some primary focus of infection has been overlooked (tonsils teeth middle ear gallbladder and so on) Pneumococcal peritonitis may be secondary to pneumococcal infection in the appendix or gallbladder, or the infection may gain entrance through the fallopian tubes Subcutaneous pneumococcal abscesses are occasionally seen in the course of a septic pneumonia at the site of hypodermic injections of camphor in oil or other oily medicaments

The role of pneumococcal infections as a cause of death has been amazingly diminished by the introduction of sulfonamide therapy This is conspicuously true in the field of pneumonia but the statement holds for other types of pneumococcal infection as well The details of sulfonamide therapy will be discussed under the treatment of pneumococcal pneumonia

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PNEUMONIA

Definition —An infectious inflammatory condition of the lung caused by pathogenic bacteria and characterized by the formation of an exudate in the interstitial and cellular portions of the lung As a result of this exudate more or less consolidation of the lung tissue takes place The clinical symp

largely to its capacity to produce pneumonia in man as well as in many of the animals Under certain circumstances however it is capable of attacking not only the lungs but almost any organ in the body

History —The pneumococcus was first isolated in 1881 by Pasteur and almost simultaneously by Sternberg in this country It was not until 1884 however that Frankel demonstrated its importance as the cause of lobar pneumonia His observations were confirmed by Weichselbaum in 1886

Bacteriology —The pneumococcus is a minute lance shaped grampositive coccus, which usually grows in pairs but sometimes, especially when cultured on artificial media in the form of chains It possesses a capsule which can be demonstrated in both body fluids and cultures The pneumococcus grows best on media containing blood or serum On blood agar plates it produces a flat grayish colony surrounded by a light green zone In plain broth, or in blood broth it grows diffusely throughout the medium The pneumococcus is distinguished from *Streptococcus viridans* by its solubility in bile and its ability to coagulate inulin The pneumococcus is extremely virulent for mice rats rabbits and monkeys On the other hand chickens and pigeons have a very high immunity against the germ The pneumococcus does not produce a toxin in the ordinary sense of the word When it is grown in media containing hemoglobin, the latter is changed into methemoglobin

Neufeld and Handel were the first to show *serologic differences* between certain pneumococcal strains and to establish two distinct types of organisms In 1913 Dochez and Gillespie by means of protection and agglutination tests subdivided all the pneumococci into four groups A somewhat similar division of pneumococci was made about the same time by Lister in South Africa Dochez and Gillespie recognized that Types I II and III were specific biologically while Type IV was a sort of waste basket group into which the remaining pneumococci were thrown In 1927 however Cooper Edwards and Rosenstein undertook a classification of the so called Group IV pneumococci Cooper and her associates were finally able to identify thirty two specific biological types of pneumococci The most prevalent of these are Types I II and III though Types IV V, VI VII VIII and XIV are rather frequently encountered in disease processes especially pneumonia The classification of pneumococci into thirty two serologic types has not exhausted the possibility of still other types A type XXXIII has already been described and not infrequently pneumococci are isolated which cannot as yet be identified as members of any generally recognized type

A good deal has been written about the *convertibility* or "mutability of one type of pneumococcus into another type either in the body or under cultivation While mutations can undoubtedly be achieved by artificial laboratory conditions it is not clear that the pneumococcus can undergo this transition under natural conditions in the animal body It should be noted however that a virulent pneumococcus under certain conditions can be transformed into an avirulent form When such a conversion takes place it is accompanied by loss of type specificity This process of dissociation is accompanied by a number of changes in the growth characteristics of the organism The virulent form is usually referred to as a smooth or S form because its colony has a smooth glossy appearance The avirulent form is called the rough or R form as its colony has a rough and dull appearance

The *chemistry* of the pneumococcus has received a great deal of investigation during the last thirty years There are three important chemical constituents the *protein* and the carbohydrate of the cell body and the polysaccharide of the capsule The carbohydrate is usually referred to as the C substance the polysaccharide of the capsule as the *soluble specific substance* or SSS The protein is apparently the same in all pneumococci, regardless of type or virulence It is capable of stimulating antibody reactions in animals but these antibodies are *lacking in type specificity* The specific polysaccharides of the capsule have received special study Each carbohydrate is distinct and specific and apparently is responsible for the serologic differentiation of pneumococci into types It has also been shown that pneumococci owe their virulence in large measure to the specific capsular polysaccharide Only virulent pneumococci produce considerable quantities of capsular carbohydrate during

Anatomic Classification—The anatomic classification of pneumonia is based upon the type of inflammatory lesion produced in the lung by the infectious agent

(1) Lobar pneumonia is characterized by a massive consolidation which usually involves all or the greater part of the lobe Frequently several lobes are involved in the process Ninety five per cent of lobar pneumonias are caused by some type of pneumococcus

(2) Bronchopneumonia is an inflammation of the terminal bronchioles and terminal air vesicles Part or all of the lobule may be involved In the majority of instances both lungs are affected with maximum involvement usually occurring at the bases Sixty to 70 per cent of bronchopneumonias are caused by some type of pneumococcus Streptococcus and other pathogenic bacteria are responsible for the remainder Suppurative bronchiolitis is an important feature in some cases of bronchial pneumonia especially those caused by the *Streptococcus hemolyticus* or *Hemophilus influenzae*

(3) Lobular pneumonia is practically synonymous with bronchopneumonia as the infection involves small groups of lobules in various parts of the lung tissue When these lobules coalesce as they frequently do into larger patches we have a condition often referred to as *confluent lobular pneumonia* and when this is sufficiently extensive it may be almost indistinguishable from lobar pneumonia

(4) Central Pneumonia.—This is usually an atypical lobar pneumonia in which the area of consolidation is situated near the hilum Because of this location frank physical signs are usually not present

(5) Interstitial pneumonia is not characteristic of any particular type of bacterial infection The pneumococcus streptococcus *Hemophilus influenzae* or even a virus may produce an interstitial type of pneumonia In interstitial pneumonia the exudate is located as the name implies in the interstitial frame work of the lung and there is comparatively little exudate found in the alveoli

(6) Aspiration pneumonia is almost synonymous with postoperative pneumonia The aspiration of material from the mouth produces a peculiar type of bronchial pneumonia not associated with any particular species of bacterial infection Contributing factors to aspiration pneumonia are surgical operations and diseases in which eructations and vomiting occur, or in patients whose tracheobronchial reflexes are dull thus allowing aspiration of regurgitated stomach contents At autopsy the aspirated gastric contents can often be demonstrated in the bronchial tree

(7) Hypostatic pneumonia is frequently seen as a terminal event in patients with longstanding heart disease or other chronic ailments conducive to chronic passive congestion of the lungs At postmortem the posterior portions of the lungs are consolidated and on section ooze large quantities of dark red bloody material The infection is terminal and usually caused by some organism of low virulence such as a higher type of pneumococcus or the *Streptococcus viridans*

Etiologic Classification—The various forms of clinical pneumonia may be classified according to the etiological agent responsible for the infection Usually a single microorganism is responsible though not infrequently two or more species may be isolated from the infected tissue

(1) Pneumococcal Pneumonia.—This is by far the commonest type of pneumonia in ordinary times In certain years there may be an epidemic of streptococcus pneumonia influenzal pneumonia or so called virus pneumonia but generally speaking pneumococcal pneumonia comprises the great bulk of acute infections of the lungs

(2) Streptococcus haemolyticus pneumonia makes up 2 to 3 per cent of the entire group though in some winters the incidence may be higher

(3) Staphylococcus aureus pneumonia is rare not over 1 per cent of all cases and is usually though not always of the bronchial type

(4) Friedlander's bacillus pneumonia constitutes 1 to 3 per cent of all cases and is characterized by a lobar type of consolidation

(5) Hemophilus influenzae pneumonia produces a peculiar type of bronchopneumonia characterized by peribronchiolitis and hemorrhagic exudate

(6) Tuberculous pneumonia may be of either bronchial or lobar type It should always be thought of in any pneumonia which is limited to one or both upper lobes

toms vary to some extent with the type of infection Pneumonia may be either primary or secondary, and the character of the lesions produced either massive or patchy

Incidence and Distribution—Pneumonia is one of the most serious infectious diseases to which man is heir It is widely prevalent in the United States Great Britain, and other civilized countries It is very difficult to estimate the incidence of the disease, but the figures on its mortality rate can be looked upon as fairly reliable For many years pneumonia ranked third as the cause of death in the registration area of the United States but examination of the accompanying chart on pneumonia mortality for New York State will show that there has been a steady decrease in the pneumonia death rate since the influenza epidemic of 1918 and that this decrease has been considerably accelerated during the last five years a phenomenon which no doubt can be attributed in part to the introduction of sulfonamide therapy At present the death-rate of 40 per 100 000 is about one fifth of the figure reported for the year 1907 an amazing decrease in fatalities from one of man's most dangerous infections

Pneumonia is particularly prevalent in cities It is a disease of the temperate zone though it may occur in the tropics A cold damp, changeable climate predisposes to the disease When it occurs in a warm climate such as that of Panama, it is doubtless referable to sudden changes of temperature Pneumonia is a disease of the late winter and early spring In New York City January February and March are the months during which the disease occurs most frequently July August and September show the lowest incidence

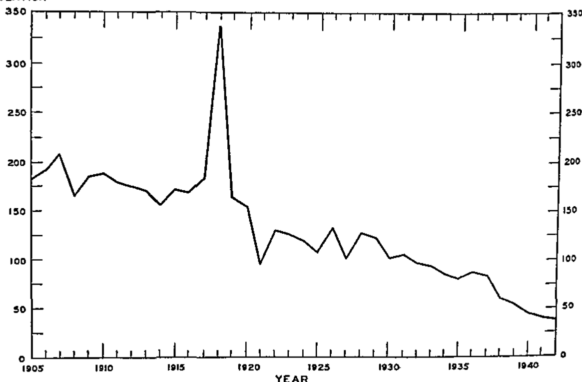


Fig 13—Trend in pneumonia mortality New York State 1905–1942

Classification of Pneumonia—The various forms of pneumonia may be subject to either an anatomical or an etiological classification Previous to the development of modern bacteriological methods physicians were dependent almost entirely on an anatomical classification In recent years however more accurate knowledge of the various bacterial agents concerned in pneumonia has led to a fairly accurate classification of pneumonia on an etiological basis

Personal Condition—Fatigue is one of the most important predisposing factors, especially when chilling of the body takes place after profuse perspiration Hunger is another important factor Debility and emaciation render individuals more susceptible to the pneumococcus In our large cities alcoholism is responsible for a great many cases

Weather—Sudden drops in temperature predispose to pneumonia—exposure to cold of any kind is undoubtedly an important factor The combination of cold and dampness such as occurs in the early spring affords conditions most favorable to contracting the disease

Previous Attacks—Pneumonia as a disease shows a definite tendency to recur but patients are usually immune to the type with which they have been infected

Acute Respiratory Infections—Pneumonia is rarely seen as a primary infection In nearly every case the patient gives a history of a preceding upper respiratory infection usually coryza or influenza sometimes tonsillitis or sore throat

Epidemiology —True epidemics of pneumonia are rare They do occur under certain unusual circumstances where large groups of susceptibles are thrown together in close personal contact particularly at the pneumonia season and directly following a widespread acute upper respiratory epidemic Examples are the epidemics among the diamond miners of South Africa and the outbreaks among recruits when a new cruiser is placed in commission

Characteristically the disease occurs sporadically one case of pneumonia here another there with no known source of infection and no known contact with another case Since a large proportion of persons harbor pneumococci it was formerly assumed that these sporadic infections must be autogenous We now know that in the great proportion of cases this does not occur It is true that in terminal pneumonia and in postoperative pneumonia the invading pneumococcus may be the same as the strain which the patient had harbored normally But in the large proportion (more than 40 per cent) of lobar pneumonia cases the invading organism is either Type I or Type II These strains are seldom found in the throat of the normal person (less than 1 in 200) The strains of pneumococci normally found in the throat are relatively avirulent types such as Types VI XI and XIX (Type III, a common inhabitant of the normal throat, is an exception to this rule)

The patient with pneumonia does not infect himself nor is he infected from contact with another case of pneumonia Where does he pick up the virulent strains? The probable source of the infection is a normal carrier We now have evidence that this indeed is the source of infection of most cases Studies of Rosenau and Felton of Stillman and of Smillie and his associates have shown that intimate family contacts of a case of pneumonia will frequently be found to harbor the homologous strain Smillie s family studies in New York in 1930 showed that from 25 to 30 per cent of family contacts of Type I or Type II pneumonia were carriers of Types I and II respectively He brings out the interesting fact that the patient does not infect the family—on the contrary the family infects the patient Often the virulent strain of pneumococcus is brought into the family by one of its working members It promptly invades the whole family One child may develop an otitis media another a sinusitis a third will develop pneumonia The sputum will be typed and this will first call the attention of the family physician to the fact that Type I pneumococcus has entered the family The patient with pneumonia usually loses his virulent strain in early convalescence but the carriers in the family may retain their virulent strains for weeks or sometimes months

The pneumonia patient in the hospital does not commonly transmit his specific strain to his nurses physician or fellow patients Simple hospital isolation procedures are quite sufficient to control the transmission of pneumococcus infection from the patient No method has yet been devised to *control transmission from the carriers* Quarantine of the family is not feasible the search for carriers by laboratory methods is not practicable Thus as Cruickshank has pointed out the epidemiology of pneumonia almost exactly parallels that of *Meningococcus intracellularis* infections and control measures also are almost identical

Morbid Anatomy —The face and lips are livid and bloody fluid may ooze from the

(7) MISCELLANEOUS INFECTIONS of the lung associated with various specific infections, e g influenza, tularemia, coccidioidomycosis, moniliasis, and others are rare forms of pneumonia usually of the bronchial type

(8) VIRUS PNEUMONIA (so called primary atypical pneumonia) is now a well recognized entity A number of different viruses have been isolated

PNEUMOCOCCAL PNEUMONIA

(Lobar Croupous or Fibrinous Pneumonia, Bronchial Pneumonia Lobular Pneumonia)

Definition —An acute infectious disease caused by the pneumococcus and characterized by massive inflammatory exudate in one or more of the lungs The dominant clinical symptoms are chill fever pain in the chest and cough with expectoration of rusty sputum

One of the most important contributions to our knowledge of pneumonia is that of Dochez and Gillespie, who found that pneumococci are made up of a number of biologically distinct strains Up to the present time thirty three biologic types have been isolated The most prevalent of these are Types I II and III though Types IV, V VI VII VIII and XIV are rather frequently encountered as the etiologic agent in pneumonia The remaining types only occasionally act as the cause of pneumonia though they are not infrequently found in the throats of healthy individuals Pneumococcus Types I to VIII cause almost 80 per cent of all lobar pneumonias as the following table will show These figures have been compiled from our own records at Bellevue Hospital

INCIDENCE OF TYPES IN 5779 CASES OF PNEUMOCOCCAL PNEUMONIA

Types	Cases	Per cent
I	1642	28 4
II	704	12 2
III	691	11.9
IV	275	4 8
V	409	7 1
VI	95	1 6
VII	358	6 2
VIII	397	6.9
IX-XXXII	1208	20 9

It is rather difficult to make a clinical distinction between the various types of pneumococcal pneumonia However, Types I II and III are prone to follow a typical course with classic lobar consolidation and a high fatality rate Pneumococcus Type I infections are commonly encountered in young people whereas Type III pneumonia is rare in the young but commonplace in middle aged or elderly people Pneumococcus Type XIV pneumonia is particularly prevalent in infants Pneumonia caused by the higher types often runs an atypical course with only partial consolidation of the lobes Many of these pneumonias caused by the higher types are true bronchial pneumonias

Factors Predisposing to Pneumonia —*Age* —The most marked susceptibility to pneumonia occurs at the beginning and toward the end of life Young children *are more susceptible than older ones* The susceptibility increases gradually during adult life, becoming greatest in old age The United States Census report shows however that 51 2 per cent of all deaths from pneumonia occur between the ages of twenty and sixty five indicating that pneumonia also takes a heavy toll of human life during the years of greatest activity

Sex —Men and women are probably equally susceptible to pneumonia when living under comparable conditions The greater incidence in the male is due to a difference in other predisposing factors such as occupation exposure, and mode of life

Race —Negroes are more susceptible to pneumonia than are the white races This was demonstrated during World War I when the Negro troops suffered much more than the white from pneumococcus infections

Occupation and Mode of Life —Pneumonia like tuberculosis is most common among the poor and undernourished Individuals who are exposed to hardships and inclement weather are particularly prone to contract the disease In the Bellevue Hospital series day laborers and sailors were the two largest groups of wage earners represented Pneumonia is more prevalent in cities than in rural districts This is probably due however not so much to living in the cities as to existence of slum conditions in the centers of densely populated areas

lung is ordinarily moist with fluid blood and dark red in color due to the general congestion The actual extent of the bronchopneumonia is indicated by the number and size of the projecting reddish gray areas which may be either isolated or in groups or may occur in confluent patches the whole producing a characteristic mottled appearance If the section has been cut in the axis of one of the lobules it may show a racemose or grapelike arrangement corresponding to small bronchi and their associated groups of air cells Between the solid areas of lung is found tissue more or less normal in color and air-containing There are also bluish depressed areas consisting of collapsed air cells whose bronchus has become plugged with exudate These collapsed areas may be large and involve a considerable portion of a lobe Occasionally the opposite result is observed and small areas of emphysema are to be seen due to inspiratory distention of the air vesicles In children there may be marked emphysema of the unconsolidated lung This helps to explain the x ray findings Commonly several solidified patches coalesce and form large masses of consolidation The process of coalescence may be so extensive as to affect whole lobes or even a considerable portion of one lung giving rise to the so-called confluent bronchopneumonia If the process is the end result of a general bronchitis the large tubes are involved in the inflammatory process and their mucous membranes are swollen and congested and the lumen contains more or less mucopurulent exudate Ordinarily the consolidated areas are polygonal in shape with a darker red center due to peribronchial congestion In the center of such a patch small grayish white points are apparent and indicate the position of the bronchioles Pressure on such solid patches causes the appearance of yellowish mucopurulent drops of exudate which can easily be squeezed from the partially plugged bronchi The walls of the small bronchioles are congested and the latter contain fluid material made up of serous exudate cells and occasionally hemorrhagic products

Microscopic examination of sections through the consolidated areas shows the bronchioles filled with mucopurulent secretion consisting of swollen desquamated epithelium leukocytes bacteria and granular material The bronchial walls are swollen and thickened and are infiltrated with polymorphonuclear and mononuclear leukocytes In certain types of bronchopneumonia such as that accompanying influenza or following measles the interstitial inflammation is marked and extends into the peribronchial and interlobular connective tissue There is always more or less denudation of the bronchial epithelium the blood vessels are engorged and here and there is to be seen an irregular dilatation of the bronchial walls

Experimental Pneumonia.—Various investigators have produced pneumonia experimentally in animals by injecting pneumococci directly into the trachea and bronchi In monkeys the disease can be perfectly reproduced by intratracheal injection of various types of pneumococci It is almost impo sible to produce pneumonia by merely introducing pneumococci into the nose or pharynx The larynx appears to form a barrier which prevents the passage of pneumococci into the trachea except under certain conditions

Pathogenesis—There are some who hold that pneumonia like certain other infections is hematogenous in origin The only evidence however in support of such a view, is afforded by the few cases in which pneumococci have been isolated from the blood before physical signs of pulmonary involvement were present In view of the difficulty often attending the detection of the earliest pulmonary lesions this evidence is not of great value Furthermore Blake and Cecil have shown that in the experimental pneumococcus pneumonia of monkeys the pneumococci may enter the blood stream following intratracheal injection in some instances before the symptoms or physical signs of pneumonia have developed Attempts to produce pneumonia in animals by intravenous or subcutaneous inoculations of pneumococci have consistently failed On the other hand the more commonly accepted view that the mode of infection is by way of the air passages has received considerable confirmation from the experimental production of pneumococcus pneumonia in animals by intratracheal inoculations Recent experimental studies by Robertson indicate that the spread of pneumonia from one lobe to

nose and mouth The striking pathologic feature of pneumonia is the consolidation of the pulmonary tissue This may be limited to *one lobe but usually in fatal* cases two or more lobes are affected According to most statistical studies the right side is more frequently involved than the left In single lobe infections the right lower and left lower are implicated with about equal frequency In two lobe infections the combination of right and left lower lobes is by far the commonest

Lobar Pneumonia—At postmortem examination the lobes involved in the pneumonic process are larger than the unaffected lobes and fill up the greater part of the *pleural space They are congested and covered* with a deposit of fibrin and on palpation are much firmer than normal lung tissue When consolidation is complete the lobe has a consistency very much like that of liver The trachea and bronchi contain blood stained viscid sputum

The process in the lung passes through a series of stages known as (1) engorgement (2) red hepatization, (3) gray hepatization and (4) *resolution Two or more of these* stages are usually demonstrable in the same case at autopsy—the reason for this being that infection starts in one lobe and as the disease progresses, spreads to other lobes In the parts first infected the process is naturally more advanced than in the parts last infected

Stage of Engorgement—This is the initial stage of the infection and is rarely *seen at postmortem The lung is still* crepitant but less so than in the healthy state There is intense congestion of the tissue which is heavier than normal On section the cut surface oozes a large quantity of bloody frothy fluid Microscopic sections show congestion of all the blood vessels and engorgement of the *capillaries in* the alveolar walls with exudation of plasma and red blood cells into the alveolar spaces *During this* stage there is only moderate infiltration of leukocytes and these are chiefly in the perivascular and peribronchial lymph spaces and in the alveolar walls

Stage of Red Hepatization—In this stage the lobe becomes completely solidified with exudate The surface is dark red and covered with *fibrin* and the lung has the consistency of liver On section the cut surface is also dark red and rather dry and granular Microscopic examination now shows the alveoli filled with fibrin, in the meshes of which there are many red blood cells and polymorphonuclear leukocytes *During this stage the cells show very little* tendency toward disintegration Many pneumococci are found in the alveoli but phagocytosis is not active

Stage of Gray Hepatization—In this stage the lobe takes on a grayish yellow color usually mottled with patches of red On section the cut surface is of the same shade and on scraping the surface with a knife a thick purulent exudate is removed *The bronchi contain purulent sputum The* grayish color is due largely to the leukocytes which in microscopic sections are found in great numbers in the alveolar spaces The red blood cells and many of the leukocytes are undergoing disintegration There are still many pneumococci in the alveoli but phagocytosis is active

Stage of Resolution—This stage like the stage of engorgement is not often seen at *autopsy When resolution is well advanced* the lobe on section has a translucent jelly like appearance and comparatively little exudate is demonstrable on the cut surface Microscopic examination shows the alveoli to be only partially filled with cells Most of the fibrin and red cells have disappeared and the leukocytes which survive are in various stages of disintegration The most characteristic feature in this stage is the *considerable number of desquamated* epithelial cells in the alveoli and the regeneration of the epithelial lining of the alveolar walls

Lesions in Other Organs—The heart is filled with fibrinous coagula The spleen usually shows moderate enlargement The liver and kidneys are the seat of cloudy swelling *In fatal cases complicating infections* of pneumococcal origin are frequently discovered in the various organs Suppurative pleuritis and pericarditis endocarditis meningitis and arthritis are among the commoner complications encountered

Bronchopneumonia—The affected portions of the *lung are somewhat fuller* and firmer than normal and in most instances firm consolidated areas can be felt throughout the lung tissue The cut surface of the

change for five to ten days In a majority of cases the disease then terminates rather abruptly by crisis or lysis in the remainder the patient dies from sepsis, toxemia or some complication

The *chill* is one of the most characteristic features of lobar pneumonia and is usually the first symptom to make its appearance A definite chill occurs in approximately two thirds of the patients while the others usually give a history of only chilly sensations The chill may be *mild or severe*, usually lasting from fifteen to thirty minutes

Pain in the chest is also a very common symptom usually appearing shortly after along on a high plateau without much variation In the less prevalent types it is often irregular in this respect resembling streptococcus pneumonia In elderly persons the temperature is lower and may run an almost normal course The degree of fever is not a reliable measure of the seriousness of the infection indeed there is some evidence that a high fever is a distinct advantage to the patient in his struggle with the disease

The *cough* at the time of onset is of a dry, hacking character unless the condition has been preceded by bronchitis when it is productive of a purulent sputum The cough is apt to come in paroxysms and cause the

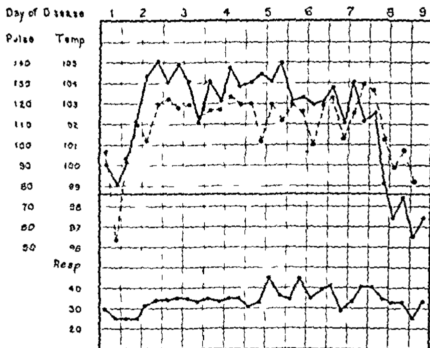


Fig 14.—Pneumococcus pneumonia Type II Crisis on eighth day Pulse curve indicated by dashes

the chill In some cases it precedes the chill and in still others the chill is absent and the disease is ushered in by the pain in the side This is usually located in the region of the nipple or at the base of the affected lung but in some cases it is referred to the abdomen and is accompanied by tenderness suggestive of appendicitis cholecystitis or peritonitis In upper lobe infections pain may be absent or referred to the shoulder

The *temperature rises rapidly* during the chill and usually *remains high ranging* between 103° and 105°F In the dominant types of pneumonia the temperature is apt to run patient much pain as the disease progresses it becomes less painful and more productive

The *sputum* in pneumonia is one of its most striking characteristics—the tenacious rust-colored sputum is pathognomonic and the diagnosis of lobar pneumonia can safely be based on its presence The character of the sputum changes as the diseases progresses From being pinkish or blood streaked at the beginning it becomes rusty and viscid on the third or fourth day Sometimes at this stage the sputum contains considerable bile which gives it a lemon or orange tinge As the disease passes into the

another is probably due to the passage of the infected exudate of the primary lesion from one main bronchus into another

Chemical Changes in the Blood—Inasmuch as the lungs are constituted to absorb oxygen and eliminate carbon dioxide, it is evident that a disease with widespread pulmonary involvement is apt to result in disturbance of these functions As far as carbon dioxide is concerned, the evidence bearing on failure of elimination is far from definite Lowering of the alkaline reserve has been frequently reported but only occasionally of more than moderate severity, whereas an actual shift of the hydrogen ion concentration of the blood to the acid side is a rare occurrence

It has been shown however that there may occur a deficiency of oxygen of such severity as to result fatally before the struggle between the forces of immunity has been decided Cyanosis has long been *prima facie* evidence of the existence of oxygen deficiency but it has been only the recognition of arterial anoxemia in quantitative terms that has led to an understanding of its importance With the introduction of arterial puncture the discovery of severe oxygen deficiency in the arterial blood of patients with pneumonia made possible the application of the physiology of 'oxygen want' previously worked out by Haldane Barcroft Schneider, and others

The arterial blood is normally 95 per cent saturated with oxygen In severe cases of pneumonia saturation of 75 per cent is not uncommon When the blood of a normal individual is lowered to this extent by breathing an atmosphere low in oxygen, a train of harmful symptoms becomes manifest The pulse rises approximately from seventy two to one hundred and twenty the patient breathes with increased rapidity *shallowness* and difficulty becomes irrational, suffers from nausea and vomiting at times becomes dizzy and feels weak and faint More severe anoxemia brings about coma, heart failure and death Mountain sickness and carbon monoxide poisoning are clinical conditions due *purely* to oxygen want In the latter the anoxemia frequently proves fatal In pneumonia symptoms of anoxemia are added to the symptoms of infection It is thus evident that arterial anoxemia may occur in pneumonia to such a degree as to have decidedly injurious effects

Other Chemical Changes in the Blood—There is considerable retention of chlorides during the active stage of pneumonia but it is not accompanied by an increase of chlorides in the blood There is also a definite increase in the amount of circulating fibrinogen

Symptoms—The symptoms of typical pneumonia vary somewhat with the age of the patient and the type of micro organism concerned in the infection There is no single symptom present in every case In the great majority of instances however the clinical picture is quite typical

The *period of incubation* is usually short probably not more than twenty four or forty eight hours In experiments on monkeys symptoms of infection appear in the animals eight to twelve hours after intratracheal injection

The *onset* is usually sudden, although occasionally it is gradual Prodromal symptoms of malaise sometimes occur but most patients are free from them and seem to be comparatively well up to the moment that acute symptoms appear For example an individual may go to bed feeling quite normal to be awakened in the night by a hard shaking chill or a sudden attack of sharp pain in the side The great majority of pneumonia patients give a history of having had an upper respiratory infection previous to the onset of pneumonic symptoms This however, may have subsided when the signs of pneumonia appeared

The *cardinal symptoms* of pneumonia are chill fever, pain in the side, cough, and the expectoration of rusty sputum Dyspnea is also a frequent symptom in the early stage The patient when seen twelve to eighteen hours after the chill is acutely ill The cheeks are flushed and the temperature is 103° to 104° F The respiration is rapid often painful on account of the pleuritic irritation The patient coughs frequently and may bring up a small amount of pinkish or rusty sputum Even when actual pain is absent the breathing is embarrassed Herpes is often present on the lip and the tongue is heavily coated If the temperature reaches 104° or 105° F the patient may become delirious These symptoms continue without much

piration decrease the cyanosis becomes less marked the cough is less distressing and is productive of considerable thick yellow sputum

Chest Signs at Onset —Inspection reveals limitation of movement of the affected side At this stage palpation and percussion are usually normal although there may be slight dulness over the involved area Pain frequently directs attention to the lobe affected and auscultation over this region reveals a characteristic feature of the early stage namely *quiet* or *suppressed breath sounds* Over the same area another early sign is the shower of fine crepitant rales heard at the end of inspiration or after coughing Bronchial voice and breath sounds are rarely heard during the first few hours of the disease

Chest Signs in a Well-developed Case —By the second or third day the typical signs of lobar pneumonia are usually present over one or more lobes Inspection of the chest reveals much less movement on the affected side The respiratory rate is rapid and accompanied by auxiliary action of the accessory muscles On *palpation* a pleural friction rub may sometimes be felt but the most important sign obtained in this way is the increased tactile fremitus on the affected side Sometimes this important sign cannot be elicited because of the accumulation of sputum in the main bronchus but this can be overcome by having the patient cough

Percussion —In the well-developed case percussion reveals dulness over the affected area In some instances the note may become almost flat differing very little from that obtained over a pleural effusion Over the uninvolved tissue just above a consolidated area percussion may elicit a note of tympanitic quality often referred to as Skoda s resonance

Auscultation —As frank consolidation develops the fine crepitant rales become less numerous and the normal vesicular breathing is replaced by bronchial breath sounds This type of breathing is very characteristic—high pitched rather harsh and with expiration of equal length with inspiration As in the case of vocal fremitus bronchial breathing may be absent or faint when the larger bronchi are completely plugged with exudate The voice sounds as well as the breath sounds usually have a frankly bronchial quality spoken of as *bronchophony* In certain cases, the voice sounds have a nasal quality—a condition termed *egophony* The whispered voice is also much intensified over the consolidated area

Chest Signs During Resolution —The respiratory rate approaches normal The dulness becomes less marked Vocal fremitus is usually slightly diminished Auscultation over the involved lung reveals many moist rales of the subcrepitant type commonly referred to as rales of resolution or consonating rales The voice and breath sounds gradually lose their bronchial quality and usually become diminished before finally returning to normal

Heart and Circulation —At the height of the disease the heart usually shows some enlargement particularly on the right side by reason of the extra burden placed upon it in forcing the blood through the congested lungs The rate is nearly always rapid and the rhythm regular Extrasystoles quite commonly occur and auricular fibrillation much less frequently The second sound over the pulmonic area is accentuated and sometimes a soft systolic murmur is heard at the apex In severe cases as the myocardium becomes exhausted by the toxemia and additional strain the heart sounds become less distinct and may take on a fetal character (embryocardia)

The blood pressure usually maintains a normal level but is apt to fall if the patient begins to lose ground A systolic pressure below 100 is a serious sign

In bronchopneumonia physical examination of the chest reveals small areas of dulness scattered throughout one or both lungs When fusion of these areas takes place the signs may assume all the characteristics of lobar pneumonia As a rule however, examination of the chest in bronchopneumonia reveals very few striking signs Over the small areas of dulness one may hear moist rales with occasional changes in the quality of the breath and voice sounds but, oftener than not dulness and rales constitute the only positive physical findings

Laboratory Findings —During recent years laboratory procedures have assumed increasing importance in the diagnosis and treatment of lobar pneumonia An early etiologic diagnosis is determined most readily

stages of gray hepatization and resolution, it becomes yellow and mucopurulent Microscopically the sputum contains mucus, red blood cells, pus cells, epithelium, and usually a considerable number of pneumococci

In bronchopneumonia the sputum is rarely rusty but in severe cases may have a frankly bloody appearance In the majority of cases the sputum in bronchopneumonia is mucopurulent In a certain number of cases of either lobar or bronchopneumonia the patient may go through the whole infection without having any sputum whatever

Dyspnea is one of the important symptoms of pneumonia The respirations are usually rapid shallow and labored and greatly aggravate the pleuritic pain The rate is almost always increased out of proportion to the amount of fever present Indeed, this type of breathing is a significant point in distinguishing pneumonia from other febrile conditions The respiratory rate usually varies from twenty five to forty per minute but may be even more when there is pain in the side or a marked grade of anoxemia A characteristic feature of the respiration is the peculiar expiratory grunt Inspiration is usually accompanied by dilatation of the alae nasi The respirations are rapid in proportion to the amount of lung involvement, they decrease in rate at the time of crisis although signs of consolidation may still be present

Herpes is observed in more than half the cases of pneumonia It appears most frequently on the lips, but may be seen about the nose on the cheeks or on the ears This symptom is often a significant one because of its early appearance and its value in differentiating between acute and chronic pulmonary disease

Nervous Symptoms —Delirium occurs in approximately 25 per cent of cases It is particularly common in alcoholic patients who in many instances must be forcibly restrained from getting out of bed Heavy drinkers often develop delirium tremens during the course of pneumonia a complication which renders the prognosis very grave It is not uncommon however particularly in mild forms of the disease for the mind of the patient to remain clear during the entire course In children the disease may be initiated by a convulsion and other cerebral symptoms strongly suggestive of meningitis Occasionally patients develop a postpneumonic psychosis in the form of a confusional insanity which, however usually terminates favorably in a short time

Gastro intestinal Symptoms —Nausea and vomiting are fairly frequent symptoms of pneumonia In some cases the illness is ushered in by an attack of vomiting Diarrhea is an unusual symptom Jaundice occurs in 5 to 10 per cent of cases The lighter form which is observed most frequently seems to have no significance—the deep jaundice which appears rarely is associated with a toxic hepatitis and makes the prognosis grave Tympanites is a frequent and troublesome symptom and is most marked in the severe cases It may be merely an expression of gastro intestinal disturbance but is more often the result of general toxemia When marked, it may add considerably to the respiratory embarrassment

In bronchopneumonia the symptoms do not differ essentially from those of lobar pneumonia The onset may be more gradual and the temperature more irregular Bronchopneumonia rarely terminates by crisis

Physical Findings —The physical signs in a typical and fully developed case of lobar pneumonia are quite characteristic but during the first twenty four or forty eight hours of the disease they may be almost if not entirely lacking With the development of specific treatment the early diagnosis of lobar pneumonia becomes more and more important and a careful search for the earliest physical signs is imperative

General Appearance —At onset the face is flushed the lips are cyanotic the skin is hot and moist herpes is frequently present on the lips or face Breathing is usually labored because of the pain in the side There is a dry hacking cough and the nostrils dilate with inspiration Frequently the patient gives a little grunt with each expiration The pulse is nearly always rapid and bounding and the rate proportionate to the degree of fever Sometimes the pulse is dicrotic but not so frequently as in typhoid fever Extrasystoles are quite common and complete irregularity is sometimes observed especially in elderly patients Toward the end of the disease in patients who are recovering the temperature pulse and res

may be occasionally permissible but should not be looked upon as a feasible routine

Other Bacteriologic Procedures —In some cases of pneumonia in which ordinary bacteriologic methods of obtaining the etio logic agent have failed the micro-organism may be recovered by cultures from some metastatic focus such as an empyema fluid or a secondary otitis or possibly an arthritis In still other cases of doubtful etiology the type can be determined by precipitin re actions with the soluble substance in the patient s serum or urine Finally there will remain a group of cases in which no pneu mococci can be isolated by any method

Blood —During the first two or three days of lobar pneumonia the total leukocyte count is usually elevated with a relative increase of the polymorphonuclear cells However it has been shown that this is not so accurate an index of the grade of infection or the amount of bone marrow response as is the increase in immature polymorphonu clear cells (shift to the left) The leukocyte count in pneumonia varies from 15 000 to 25 000 with the polynuclear cells ranging from 80 to 90 per cent Counts above 30 000 with the percentage of polynuclear cells in the nineties suggest some suppurative com plication such as empyema In severe over whelming infections some patients show a leukopenia from the first day of the disease In other instances patients who have been running a leukocytosis develop a terminal leukopenia during the last few hours of life In either case leukopenia is of grave import and indicates marked toxic depression of the bone marrow function

Dochez found that during the acute stage of pneumonia the coagulation time of the blood is usually prolonged There is also an increase in the quantity of circulating fibrin ogen and a sharp elevation of the sedimen tation rate of the red blood corpuscles

Palmer has shown that in lobar pneu monia there is an increase of excretion of total acids in the urine—not sufficient in amount however to indicate any marked degree of acidosis

Blood Culture —Pneumococci can be dem onstrated in the blood in approximately one third of all cases of lobar pneumonia The percentage of positive blood cultures in bronchopneumonia is considerably lower The prognosis in pneumonia is closely re-lated to the degree of bacteremia present Also its significance becomes greater when the bacteremia occurs late in the disease For example the presence of a few organ-isms in the blood early in the infection does not give as serious an outlook as does a late blood stream infection particularly when it is severe Under any conditions bacteremia indicates a grave situation and it is usually observed in connection with extensive lung involvement

Urine —In pneumonia the urine is scanty highly colored and of high specific gravity It usually contains a trace of albumin and in many cases a few casts These findings however as in many other febrile conditions simply indicate a toxic irritation of the kid neys In addition the urine shows a marked decrease in the content of chlorides—as much as 10 Gm of sodium chloride may be retained in the body during the course of the disease During convalescence there is usu ally an increased excretion of chlorides

X-ray Findings.—Usually by the time the patient has been admitted to the hospital and x ray examination has been made a dense homogeneous shadow is seen over the lobe or lobes involved This picture is fre-quently seen before physical signs of con solidation have appeared Where it has been possible to obtain repeated x ray plates early in the disease the shadow appears to extend from the hilum and spread out until it in volves the entire lobe Chest x rays show that frequently the diaphragm is elevated on the affected side and also indicate some en largement of the cardiac shadow Fluoro scopic examination shows limitation of the movement of the diaphragm on the side of the disease As the infection clears up the shadow slowly becomes less dense and less uniform Mottling of the affected lobe usu ally remains for some time after the toxemia and the signs of consolidation have entirely disappeared

Course and Termination —The fever persists for from five to ten days sometimes even longer During this time the tempera ture is often remarkably constant varying between 104° and 105° F day after day In old people the temperature is frequently lower and more irregular than in children and young adults

by bacteriologic study of the sputum Blood cultures are also considered a valuable aid both in diagnosis and prognosis The leukocyte count has acquired greater significance since the introduction of the Schilling index X ray examination is frequently employed and with the improvement in portable apparatus is found to be of great value in following the course of the pulmonary lesion

Sputum—The first step in the examination of the sputum should be a careful study of its gross characteristics It has been noted that in lobar pneumonia the expectoration usually has a typical rusty tenacious appearance Sputum from a case of bronchopneumonia is frankly purulent or it may be salivary in character A microscopic examination of direct films of the sputum should be made in order to rule out an acid fast infection and to note the predominance of a particular organism The sputum in pneumonia usually contains large numbers of pneumococci and because of this fact it is by studying the sputum that the bacteriologist determines the type of pneumonia with which the patient is infected The various laboratory procedures for typing pneumococci need not be described in detail The method now in common use is known as the Neufeld method it was first described in 1902 but did not come into general use until recently The reliability of the Neufeld method of typing has now been established by a number of observers

Neufeld Method—In carrying out the test a small loopful of sputum is smeared on a glass slide Quickly add to this two loopfuls of undiluted type specific rabbit serum and two loopfuls of Loeffler s alkaline methylene blue A thorough mixing is essential In many laboratories the sputum is tested for only the commoner types (I to VIII inclusive) If the specimen is to be tested against the entire thirty two types several combinations of monovalent antisera are first mixed and then added to the sputum Examination is made under the oil immersion lens with a strong light partially dimmed When pneumococci are mixed with a homologous antiserum the swollen sharply outlined capsules present an unstained greenish gray ground glass appearance In negative smears the pneumococci show no capsule or only a faint halo of light It is well to reserve final reading of the reaction for half an hour after the preparation has been made Typing by the Neufeld method should if possible be done on fresh sputum though reactions can still be obtained in sputums twenty four or even forty eight hours old If delay is inevitable the specimen should be stored in a refrigerator to prevent overgrowth by other bacteria

Other Methods of Typing—The Mouse Method—In some cases because of the scarcity of pneumococci in the sputum it may be impossible to determine the type of infection without first increasing the number of organisms In such cases it is well to inoculate a white mouse About 0.5 cc of sputum previously washed with sterile salt solution is injected into the peritoneal cavity of the mouse Three to four hours later the Neufeld technic is applied to small drops of the peritoneal exudate withdrawn by means of a sterile capillary tube or hypodermic syringe If pneumococci are still not present in sufficient numbers the procedure is repeated every hour until diagnosis can be made If only a small amount of peritoneal exudate is available preliminary tests should be restricted to those types for which therapeutic serum is available

Cultural Method—If a mouse is not available a tube of Avery's glucose blood broth is inoculated with some of the washed sputum After incubation for four to six hours it may be possible to determine the type of pneumococci in the culture by the Neufeld method

Throat Swab Method—When no sputum is available the type of pneumococcus may be determined by examination of material obtained on a throat swab By making the patient gag a small amount of mucus can often be caught on the end of a swab and smears made directly from this Some prefer to drop the swab at once into a test tube containing 2 to 3 cc of glucose blood broth and send the culture to the laboratory where after four to six hours of incubation the pneumococci present in the culture may be typed by the Neufeld method

Lung Puncture—Some writers recommend lung puncture when other methods of determining the type fail Such a procedure

cases x ray and fluoroscopic examination are of the greatest aid In all cases of empyema the diagnosis is finally determined by exploratory aspiration

Empyema should be regarded as a complication (1) occurring coincidentally with lobar pneumonia (2) occurring as one of a chain of complications including septicemia meningitis endocarditis pericarditis etc or (3) following pneumonia as a sole complication The seriousness of the condition *depends largely upon which one of these* situations is present When it appears early in the course of pneumonia the outlook is much more grave than when it occurs late or follows the disease When it is one of a chain of complications the prognosis is usually hopeless

SURGICAL TREATMENT is usually indicated in empyema A procedure which is now commonly used is the so called closed tube drainage in which a tube is inserted into the seventh or eighth intercostal space in the posterior axillary line The pus is allowed to drain slowly and when the cavity has been emptied it is irrigated every four hours with normal saline solution In cases in which the pus is too thick for satisfactory drainage irrigation with Dakin s solution is started at the time of the operation Encapsulated empyema may be treated in the same way However many surgeons feel that thoracotomy and open drainage is the procedure of choice in these cases Empyema when it occurs early and the exudate is thin as in hemolytic streptococcus infections may be treated by repeated aspirations followed by closed tube drainage when the pus becomes thick

Pericarditis is a serious complication of pneumonia occurring in 1 to 2 per cent of the cases It almost invariably terminates fatally The diagnosis is difficult to make for the symptoms and signs of pneumonia overshadow those of pericardial involvement. A friction rub synchronized with the heart beat and associated with pericardial pain is highly suggestive particularly if the rub persists when the patient is holding his breath In some cases a pericardial effusion may be detected but this will rarely be recognized without x ray photographs of the chest The treatment consists in removing the fluid by tapping and by surgical measures as indicated Pericarditis is one of the more serious complications of pneumonia The diagnosis is seldom made except at postmortem examination In a series of 131 fatal cases of Type I and Type II pneumonia, suppurative pericarditis was found four times Fibrinous pericarditis is a rather common incident in the course of pneumonia, but is of comparatively little clinical significance This is recognized by the presence of a transient pericardial friction rub

Endocarditis is also a comparatively rare complication and probably always fatal This condition may develop during the course of the pneumonia or it may come on gradually several days after the temperature has become normal It is more likely to occur in patients with chronic valvular heart disease Like other types of malignant endocarditis it runs a swift septic course with spiked temperature rapid pulse and often with chills and sweats The lesions are usually on the mitral valve although other valves may be involved Physical examination reveals a loud systolic murmur which increases in intensity as the disease progresses Signs of embolism appear in the different organs from time to time

Meningitis like pericarditis and endocarditis is rare and usually fatal It is often associated with the chain of severe pneumococcal complications which follow septicemia The prognosis in pneumococcus meningitis when treated with serum or sulfapyridine or both is not quite so hopeless as it previously was Indeed pneumococcus meningitis occurring as it frequently does in children in the absence of pneumonia is often curable by modern methods of treatment As a complication of pneumonia, meningitis is still of very serious import, though a few cases have been saved by sulfonamide therapy

Pneumococcus arthritis is a rare complication It develops only in cases with pneumococcus septicemia The condition is usually monarticular and generally takes on the character of a surgical joint In some cases however the joint does not suppurate and the condition clears up spontaneously

Thrombosis and embolism are both rare complications and usually occur in the femoral vessels Pulmonary infarcts occasionally are the cause of sudden death The

Pneumonia may terminate by crisis or lysis The typical crisis of pneumonia is one of the most striking features of the disease The patient struggling against a virulent infection, often appears on the verge of col lapse The whole organism seems to be af fected by the toxemia Suddenly the patient begins to perspire freely, there is a rapid drop in temperature to normal or subnormal, accompanied by a corresponding fall in the respiratory and pulse rate In a few hours the entire clinical picture is changed The patient looks and feels much better and drops off into a quiet sleep In some cases the true crisis is preceded by the so called pseudocrisis The temperature drops to normal or almost normal then rises again to 102° or 103° F for twenty four hours when the true crisis occurs

In many cases there is no definite crisis but the patient's temperature comes down gradually by lysis Both crisis and lysis ap pear to be an expression of acquired im munity on the part of the patient This opinion is corroborated by the fact that the various immune bodies make their appear ance in the blood of the patient at the time of crisis or just after it

In cases that terminate fatally the tem perature remains high the pulse becomes rapid and weak and the respiratory rate is accelerated These phenomena are referable usually to spread of the pneumonic process from one lobe to another until 3 4 or even all 5 lobes are involved in the infection The cyanosis becomes more marked the blood pressure falls and the patient shows every evidence of an extreme toxemia Blood cul tures taken at this time are usually positive and in most instances there is a drop in the total leukocyte count The immediate cause of death in pneumonia is usually circulatory failure which is presumably the result of vasomotor paralysis In some instances death appears to be referable to respiratory failure Various complications traceable to pneumococcal origin such as endocarditis pericarditis and meningitis are the immedi ate cause of death in not a few cases

Complications in pneumonia are numer ous and may be divided into two groups—those directly referable to the pneumococcus and those of toxic or other origin

Acute fibrinous pleurisy occurs so frequently in pneumonia that it can hardly be called a complication The characteristic friction rub of dry pleurisy is noted early in the disease in a good many cases and often causes the patient great discomfort Later on the fibrin may form a thick tena cious layer over the entire surface of the affected area

Pleurisy with Effusion —Acute serofibrin ous pleurisy is also a common complication of pneumonia It may develop early in the disease but is more apt to make its appear ance late in the course sometimes even after the crisis The presence of a pleural effusion is usually, but not necessarily indicated by some rise in temperature The physical signs are those of fluid in the chest If any con siderable amount of fluid collects, it should be aspirated

Empyema is the most frequent severe complication of pneumonia In the Bellevue Hospital series 5 1 per cent of the pneumo coccal pneumonias developed empyema The incidence of empyema was highest in Type I pneumonia, as the following figures show

	Cases	Percentage with empyema
Pneumococcus Type I	644	6 8
Type II	368	3.5
Type III	268	3 7
Misc types	633	5 0

Occasionally empyema of *Streptococcus haemolyticus* origin complicates a pneumo coccus pneumonia but this is rather rare

Pneumococcus empyema differs from that caused by the *Streptococcus haemolyticus* in that it usually develops after the more acute symptoms of pneumonia have subsided Empyema should be suspected in any case when after a day or two of normal or nearly normal temperature a fever of several de grees again makes its appearance accom panied by increase in pulse and respiratory rate and by a polymorphonuclear leukocy tosis Physical examination reveals the signs of fluid—absence of vocal fremitus flatness on percussion and diminished or absent voice and breath sounds Sometimes a pocket of pus develops between two lobes or in a small sacculated area This condition is known as *encapsulated empyema* The diagnosis is difficult particularly when the amount of pus present is very small In such

predisposes to another There are reports in the literature of patients who have had 20 or 30 attacks of the disease In our experience recurrences have usually been due to different types of pneumococcus Individuals have been followed who have had repeated attacks of pneumococcus Type III pneumonia In such cases a chronic focus of infection possibly in one of the sinuses should be looked for In a recent study by Strauss and Finland there seemed to be a greater tendency to recurrences at shorter intervals and from the same type of pneumococcus in patients who had been treated with sulfonamides than in patients not so treated

Special Clinical Varieties of Pneumonia —*Abortive Pneumonia*—Pneumonia occasionally runs a very short course—sometimes only twenty four to forty eight hours The early administration of serum or sulfonamides often produces this clinical picture

Pneumonia in the Aged—The onset is often insidious and the temperature may be normal or only slightly elevated The physical signs may be frank or very indefinite These patients often die suddenly of heart failure either during the infection or sometimes several days or even weeks after all signs of pneumonia have disappeared

Pneumonia Secondary to Other Diseases —A terminal pneumonia is seen very frequently in the course of chronic cardiac and renal disease diabetes pernicious anemia and other diseases In the Bellevue Hospital series 32 6 per cent of the cases occurred in patients with some chronic systemic disease The death rate in these cases was 46 4 per cent

Pneumonia is frequently seen as a complication of other infectious diseases particularly influenza and measles The lobar type of secondary pneumonia is nearly always of pneumococcal origin Pneumococcal pneumonia is rarely found as a complication of chronic pulmonary tuberculosis

Postoperative pneumonia is a secondary condition due either to the aspiration of mucus and saliva into the air passages or to the irritating effect of the anesthetic on the bronchial mucous membrane Many of these cases should not be classed as postoperative pneumonia but as postoperative atelectasis Pneumococci of the less virulent types are usually isolated from the sputum These postoperative pulmonary conditions usually run a mild and atypical course

The *tubercle bacillus* is capable of producing a lobar type of consolidation Lobar pneumonia of tuberculous origin may run a course quite similar clinically to that of pneumococcus pneumonia In the majority of instances however tuberculous pneumonia terminates fatally

Diagnosis —In a typical case of pneumonia the diagnosis can usually be made within a few hours after onset although the characteristic physical signs may not have made their appearance A patient suddenly taken with chill followed by fever herpes cough dyspnea and pain in the side presents a picture which can hardly be mistaken for any other condition There are a certain number of cases however usually secondary to some mild respiratory infection in which the onset is gradual and in which the more characteristic symptoms may be entirely absent Lobar pneumonia may develop without chill or pain in the side even the cough and expectoration are sometimes absent In cases of this type rapid respiration associated with cyanosis is a suggestive combination of symptoms As has been stated before the respiratory rate in pneumonia is nearly always out of proportion to the degree of fever One of the most convincing evidences of lobar pneumonia is the typical rusty sputum which is practically never seen in any other condition

It is important for the student of medicine to recognize the early symptoms and signs of pneumonia in order that specific treatment may be applied promptly Slight dulness a few moist rales and diminished breath sounds may be the only local signs during the first twenty four or thirty six hours of the disease Of these signs suppressed breathing is perhaps the most important By the third day frank signs of consolidation are usually present—increased vocal fremitus dulness and bronchial voice and breathing

The diagnosis of bronchopneumonia often presents a more difficult problem than that of lobar pneumonia for the clinical picture may be less typical As a rule the diagnosis of bronchopneumonia may be safely made when the temperature and respiration rate

two instances of this complication in the writer's experience have both occurred during convalescence

Pneumococcus peritonitis was seen in only three of the Bellevue cases All three patients died

Pneumococcus abscesses of the skin are occasionally observed but usually skin infections encountered in pneumonia are of staphylococcal origin

Associated Conditions—In addition to the above described pneumococcus complications there are a number of other conditions frequently seen in association with lobar pneumonia

Lung abscess is not so common a sequel of lobar pneumonia as is generally supposed When present, it is usually due to bacteria other than the pneumococcus—in most cases, to staphylococci and the fusospirochetal organisms In 2122 patients with Type I and Type II lobar pneumonia observed in the wards of Bellevue Hospital lung abscess occurred in only nine

Acute Nephritis—Many patients show signs of renal irritation, such as the presence of albumin and casts in the urine, but genuine nephritis is a rare complication

Parotitis occurred in seven of the Type I and Type II Bellevue cases and in those where cultures were taken the infection was of staphylococcal origin Osler says that parotitis is commonly seen in association with endocarditis where it is presumably a pneumococcus infection This does not agree with our experience though it has usually occurred in severe types of pneumonia The death rate in the Bellevue cases was 70 per cent In our series drainage by massage gave better results than surgical intervention

Otitis Media is the most frequent complication of pneumonia in children This condition is usually not a serious one and appears rather as an incident in the course of the disease Otitis media rarely occurs in adult pneumonia

Atelectasis of one or more lobes of the lung due to obstruction of a main bronchus with sputum or mucus is sometimes revealed by x ray or fluoroscopic examination Radiographs show the diaphragm to be elevated and the mediastinum retracted toward the collapsed lung When this condition occurs coincidentally with pneumonia it is serious when it occurs after the infection has subsided as is most frequently the case it merely retards convalescence Special treatment for this complication is usually unnecessary although in some cases bronchoscopic removal of the plug from the bronchus may give spectacular results

Unresolved Pneumonia—Delayed resolution is a sequel of pneumonia which may occur at any age, but is seen chiefly in elderly patients In the average case of pneumonia the signs in the lungs usually clear up completely within a week or ten days after crisis In the Johns Hopkins series of Osler 3 to 4 per cent of patients showed delayed resolution In most cases the signs persist for two or three weeks but in some instances they continue for several months During this period the temperature is normal, or only slightly elevated The patient has no particular discomfort but the strength and weight do not return to normal Physical examination usually shows bronchial breathing associated with moist rales but sometimes the bronchial breathing disappears and only the dulness and rales persist

Chronic Interstitial Pneumonia—Occasionally a patient with delayed resolution fails to recover and the condition passes into a chronic interstitial pneumonia the symptoms of which are described elsewhere

Relapse and Recurrence—Relapse is not common in pneumonia Subsequent to the first attack the temperature may remain normal from one to ten days or even two weeks Relapses in pneumonia are usually but not always caused by a type of pneumococcus different from that of the first attack The severity of the relapse naturally depends on the character of the second infection Relapses are usually seen in hospital wards where the new infection is picked up from some neighboring patient *Streptococcus haemolyticus* pneumonia secondary to pneumococcus pneumonia was frequently observed during World War I We have seen a number of relapses in patients who had received inadequate doses of serum or sulfonamide therapy

Recurrence is more frequently observed in pneumonia than in any other acute infectious disease By reason of this fact the impression prevails that one attack actually

it is intensified In pneumonia the voice and breath sounds are loud and tubular, in pleural effusion they are diminished In children however pleural effusion may present nearly all the signs of a pneumonic consolidation It must not be forgotten that pneumonia and pleurisy may coexist

Tuberculous pneumonia may closely resemble lobar or bronchopneumonia of pneumococcal origin in the character of the onset symptoms and physical signs and in many cases it is impossible to distinguish between the two conditions until a week or two has elapsed The history of pre-existing tuberculosis or involvement of the upper lobes suggests tuberculous pneumonia A high leukocyte count may be seen in both conditions Sooner or later the patient expectorates large quantities of purulent sputum in which tubercle bacilli can readily be demonstrated

Pulmonary infarction may simulate lobar pneumonia especially when the infarct is of considerable size In patients with chronic cardiac disease the diagnosis of lobar pneumonia should never be made until pulmonary infarction has been excluded The latter condition is not so apt to be ushered in with a chill the fever is not so high and there is not so much change in the leukocyte count In pulmonary infarction the sputum is bloody rather than rusty Pulmonary infarcts sometimes become infected and develop into frank pneumonic processes

Lung Abscess—In its early stages lung abscess may be indistinguishable from pneumonia When an abscess ruptures into a bronchus the sputum is usually profuse and of foul odor A history of aspiration of a foreign body or of a recent operation on the upper respiratory tract points to an abscess An x ray of the chest will usually settle the point but not always A week or ten days may elapse before the abscess takes on its characteristic clinical picture

Pneumonia is sometimes mistaken for *appendicitis* and *cholecystitis* in cases where diaphragmatic pleurisy is present In such cases the pain is referred to the abdomen and there may be considerable abdominal tenderness and rigidity

Prognosis—The fatality rate in pneumonia depends upon a great many factors In the large city hospitals of both Europe and America the mortality rate is usually in the neighborhood of 30 per cent In Bellevue Hospital the records show that the death rate has varied considerably from year to year ranging from 30 to almost 50 per cent In recent years the fatality rate has been dropping rapidly, due largely to the introduction of sulfonamide therapy

The fatality rate in private practice is distinctly lower than that in hospitals This is due of course to the fact that mild cases are treated at home while severe ones are sent to hospitals

Age of Patient—Youth is the greatest of all assets in pneumonia In children between two and ten years old the death rate is less than 10 per cent and the figure is no higher for patients in the second decade of life In hospital practice the mortality rate tallies closely with the age of the patient that is 20 per cent between the ages of twenty and thirty 30 per cent between thirty and forty and so on Comparatively few patients more than seventy survive the disease The fatality rate for bronchopneumonia in infants less than two years of age has always been high This however like the fatality rate for other age groups is being greatly reduced by sulfonamide therapy

Type of Infection—The prognosis in lobar pneumonia is definitely related to the type of pneumococcus responsible for the infection In the accompanying table the death rate for the various types has been determined by compiling figures from the reports of various writers including our own studies at Bellevue Hospital It will be noted that the three most prevalent types of pneumonia (Types I II and III) have the highest death rates The high death rate for Type III pneumonia can be attributed in large part to the high incidence of Type III pneumonia in elderly people Type III pneumonia in young people is not especially malignant The less prevalent types are distinctly milder in character The figures in the table below do not include any cases treated with serum or sulfonamides

Extent of Infection—The prognosis in lobar pneumonia is much less serious when the infection is confined to one lobe In our cases the death rate in one-lobe infections was only 20 9 per cent while that for multilobar infections was 40 per cent

are increased and localized rales are heard in the lungs The insidious onset of bronchopneumonia, its secondary character remittent type of fever, the fine moist rales and the absence of high pitched tubular breathing are important differential points in distinguishing it from lobar pneumonia

The laboratory aids in the diagnosis of pneumonia are (1) typing of the sputum, (2) blood culture (3) leukocyte count (4) x ray examination The first three of these are indispensable to the proper handling of the case X ray examination is of great help in certain cases but is not necessary as a routine procedure Sputum typing should be are taken under sterile precautions and transferred to a suitable blood culture medium usually plain beef extract broth If possible, it is well to plate out 1 or 2 cc of the blood with agar, in order to determine the number of colonies of pneumococci per cubic centimeter of blood

Differential Diagnosis—*Influenza* and *acute bronchitis* may be easily confused with a mild pneumonia, particularly at the outset Either one may start with a chill They are characterized by fever muscular aching and cough However, the sputum is not rusty and pleural pain is almost never seen The physical examination of the chest will



Fig 15—G D age forty three years Lobar pneumonia pneumococcus Type II X ray shows consolidation of right lower and lower portion of right upper lobe

carried out as soon as the clinical diagnosis of lobar pneumonia has been made In upper lobe infections the physician should always eliminate the possibility of a tuberculous lobar pneumonia by examination of the sputum for tubercle bacilli Blood culture is of valuable aid in the diagnosis and prognosis of pneumonia It is the best check on the sputum typing It is the best index to prognosis as patients with positive blood cultures have a fatality rate four times higher than patients with negative blood cultures A positive blood culture by reason of its serious import is an indication for intensive specific therapy Five cc of blood be negative except for occasional sibilant or sonorous rales The leukocyte count is normal or only slightly elevated In case of doubt an x ray of the chest should settle the question

Pleurisy is often confused with pneumonia especially when there is pleural effusion In both pneumonia and pleurisy the affected side shows some degree of immobility and there is dulness on percussion but in pneumonia the intercostal spaces are not obliterated the heart is rarely displaced and the dulness is not absolute Most important of all vocal fremitus is decreased or absent in pleurisy with effusion while in pneumonia

to relieve the pain but to give the patient rest and sleep The former prejudice against the use of morphine in pneumonia was probably not justified Most modern writers on the subject look upon morphine as perhaps the most important remedy at hand for con trolling pain restlessness delirium and other untoward symptoms It is contraindi cated however in patients showing an ex cess of moisture in the lungs Cough is often a troublesome symptom and like pain is best controlled by codeine or morphine Some practitioners advocate ammonium chloride or ipecac as an expectorant when the cough is dry Restlessness and insomnia may be relieved with sodium bromide phenobarbital or some of the other barbiturates If the pa tient becomes actively delirious paraldehyde or morphine is preferable Abdominal dis tention is encountered in nearly every severe case of pneumonia It must be attacked promptly in order to remove the extra burden which it places on the circulation and respiration In many cases proper at tention to the bowels will prevent distention Enemas are usually preferable to cathartics and a soapsuds enema is recommended once every twenty four hours When distention is marked the enemas should be supplemented by turpentine stupes and hypodermic in jections of surgical pituitrin in doses of 0.5 to 1 cc It is also advisable to insert a rub ber tube into the rectum preferably imme diately following an enema to facilitate the passage of gas Hyperpyrexia and the de lirium which often accompanies it may be relieved to some extent by sponge baths

Oxygen Administration —The rational method of treating cyanosis and dyspnea in pneumonia is by the administration of oxy gen It is known that the degree of cyanosis is usually inversely proportionate to the oxygen saturation of the arterial blood and further that in many cases the inhalation of 40 to 50 per cent oxygen raises the per centage of saturation to normal or nearly normal It has already been pointed out that many of the distressing symptoms of pneu monia and consequently the prognosis are closely related to the amount of anoxemia the relief of which is accompanied by definite beneficial effects Within two or three hours after the treatment is instituted the cy anosis disappears or greatly diminishes the patient becomes quiet and more comfortable (frequently sleeping for the first time in many hours) respiration is slower and deeper the pulse is decreased sometimes the temperature drops a degree or two A change in mental state is frequently observed This symptomatic relief, which frequently occurs demonstrates the value of oxygen In some cases oxygen therapy seems to prolong life until the patient develops an immunity against the infection and for this reason it is believed to be a life saving measure

At the present time there are four satis factory methods of administering oxygen They are (1) the *nasal catheter* or *metal cannula* in combination with a high pressure oxygen supply and a reducing valve (2) the *portable oxygen tent* (3) the *oxygen chamber* and (4) the *oxygen mask* or *hood* Each method has its advantages and dis advantages

The *nasal catheter* is the simplest the most economical and the most readily avail able The catheter should be of small size lubricated with petrolatum and perforated at the end by five or six small holes so that the stream of oxygen is not continu ously directed against a small area of the mucous membrane The tip of the catheter should be withdrawn about ½ inch from the nasopharynx to prevent irritation and the outer portion securely fastened to the side of the cheek or forehead with adhesive tape When four to five liters of oxygen per min ute is administered through the catheter a concentration of 35 to 37 per cent is obtained in the inspired air which is often sufficient to give symptomatic relief When the nasal catheter is inserted through the nostril and down the posterior wall of the larynx to a point opposite the glottis or the uvula the oxygen concentration of inspired air is higher by at least 5 per cent than when the catheter is placed in the nasopharynx Thus 5 liters of oxygen per minute will give an oxygen concentration of 45 per cent in the inspired air and 7 liters of oxygen per minute will provide an oxygen concentration above 50 per cent With proper care in the placement of the catheter in the oropharynx barely short of the point at which swallowing the gas occurs during deglutition relatively high concentrations of oxygen can be maintained in the inspired atmosphere

FATALITY RATE FOR FIRST EIGHT TYPES OF PNEUMOCOCCAL PNEUMONIAS*

Types	Cases	Deaths	Per cent
I	762	288	37 7
II	557	258	46 3
III	999	474	47 4
IV	166	42	25.3
V	254	73	28 8
VI	68	18	26 4
VII	227	50	22 0
VIII	295	55	18 6

None received serum or sulfonamides

BACTEREMIA —This complication may occur in pneumonia of any type and renders the prognosis much more serious At Bellevue Hospital the death rate in Type I pneumonia with bacteremia was 66 7 per cent in Type II septic cases it was 87.5 per cent The corresponding figures for patients whose blood remained sterile were 22 per cent for Type I, and only 8 5 per cent for Type II Septicemia is so commonly associated with fatal lobar pneumonia that a patient s chances for recovery might almost be said to depend on the prevention or relief of this condition Not only is the fatality rate related to the presence or absence of bacteremia but it is also dependent in great measure upon the number of organisms present in the blood stream For example in a large series of Type II patients receiving no specific treatment there were only three with more than five organisms per cubic centimeter of blood who recovered

Other Factors in Prognosis—RACE and SEX appear to have very little influence on the death rate of pneumonia It has been claimed that the death rate is higher in the Negro than in the white race but these figures have been questioned

HABITS —It is needless to say that a patient s habits play an important part in prognosis In the writer s series the death rate from pneumonia in alcoholics was 56 per cent almost twice as high as that for the cases in which alcoholism was not a factor Patients in good physical condition have a much better chance than those who have been exhausted or worn out by some previous illness or by overwork Correspondingly the patient s station in life is significant Patients in the higher walks of life being well fed and clothed and usually in good physical condition are a better risk than those who are poor underfed and ill clothed

Treatment —The treatment of pneumonia is governed by the general principles that apply to the treatment of all acute infectious diseases The treatment is concerned with (1) general care of the patient, (2) relief of distressing symptoms and (3) measures for overcoming the infectious agent

General Care of the Patient—The first essential in the proper care of a patient with pneumonia is good nursing There is probably no disease in which the services of a competent well trained nurse are more valuable The patient must be kept quiet and as comfortable as possible Everything should be done to encourage relaxation and sleep and to keep up the patient s morale The sick room should be properly ventilated but the patient must be kept warm and well protected from drafts During the acute stage, the patient should be forced to take plenty of fluid particularly water, although such beverages as weak tea, ginger ale Vichy or other waters are sometimes more palatable to the patient and should be allowed As much as three liters of fluid should be given in the twenty four hour period The diet does not play as important a part in the treatment of pneumonia as in certain other infections The disease usually runs a short course so that a high caloric intake during the acute period is not required indeed in some instances it may harm the patient by causing distention A liquid diet is usually preferable the basis of which should be milk cream broth and fruit juices

Symptomatic Treatment—In the mild infections the treatment of symptoms may be entirely unnecessary but in severe cases it becomes one of the physician's most important duties How to relieve the pleuritic pain is one of the first problems that arise Occasionally the pain is alleviated by counterirritation in the form of an ice bag hot poultice or mustard plaster A chest binder is preferable to adhesive plaster for immobilizing the chest Codeine 0 03 to 0 06 Gm (½ to 1 grain) by mouth is often helpful but in cases where the pain is very severe morphine in small doses 0 008 to 0 01 Gm (⅛ to ⅙ grain) hypodermically should be used without hesitation not only

by Whitby in 1938, when he showed its remarkable protective power in mice against various types of virulent pneumococci

Soon after publication of Whitby s experiments a clinical report was made by Evans and Gaisford on the effect of the drug on pneumonia in man These writers noted a fatality rate of only 8 per cent in their 100 cases of pneumococcal pneumonia treated with sulfapyridine while the control group of untreated cases showed a death rate of 27 per cent It was soon discovered however that sulfapyridine though possessing remarkable value in controlling pneumonia had certain practical disadvantages Its ingestion caused intense nausea and vomiting in a considerable proportion of patients and produced other toxic effects which soon led to a search for a less objectionable agent

Sulfathiazole another sulfonamide derivative was introduced in 1939 and it soon became evident that it possessed definite advantages over sulfapyridine Only 25 per cent of patients receiving sulfathiazole became nauseated and the degree of conjugation of the drug in the blood and urine was much less than that which occurred with sulfapyridine As a result a larger proportion of the drug absorbed into the blood stream was therapeutically active Numerous clinical reports have indicated that from the therapeutic standpoint sulfathiazole is equally as efficient as sulfapyridine in controlling pneumococcal infections

In 1940 sulfadiazine another sulfonamide derivative was introduced by Roblin and his co workers Laboratory studies indicated that sulfadiazine had even less toxicity than sulfathiazole and sulfapyridine and was equally as effective against experimental pneumococcal infections At the present time sulfadiazine is the most popular of the sulfonamide drugs for the treatment of pneumonia although for economic reasons sulfathiazole is still being widely used It is now universally conceded that the results obtained by these three forms of sulfonamide therapy are about equally good the prompt administration of any one of the three will reduce the usual pneumonia death rate of 30 per cent to approximately 6 or 7 per cent In the case of all three drugs a considerable inactive fraction accumulates in the blood in the form of conjugated or acetylated salt Due to this fact it is impossible to foretell from the amount of the drug administered the actual blood level of the active unbound drug It may vary widely due to the difference in the amount of drug conjugation in different subjects The ideal blood level of free drug has not yet been established but it is probably somewhere between 6 and 12 mg per 100 cc of blood

The conjugated acetylated form is entirely useless so far as having any effect on the pneumococcus is concerned and furthermore it has the disadvantage of being so insoluble that it tends to precipitate in the kidneys ureters and bladder of animals which have received the drug Not infrequently the acetylated salt is demonstrable in the urinary tract of human subjects Blood determinations should be made at frequent intervals during the administration of the drug to be sure that an adequate blood concentration has been reached The methods of either Marshall or Werner may be used for this purpose

Sulfadiazine being the drug of choice the remainder of this discussion on sulfonamide therapy will be confined to sulfadiazine except where otherwise indicated It should be added that the use of sulfapyridine has now been almost completely discontinued because of its toxic effects

Outline of Sulfadiazine Therapy — The initial dose of sulfadiazine should be 2 to 4 Gm (30 to 60 grains) by mouth followed by 1 Gm (15 grains) every four hours day and night until the infection is well under control It is customary to continue this dosage for 24 to 72 hours after the temperature has reached normal The drug can then be discontinued or cut to half the previous dose or the regular dose can be continued every six to eight hours instead of every four hours After twenty four hours of half doses it is usually safe to discontinue the drug altogether In severe infections with bacteremia or extensive bilateral involvement it is advisable to continue full doses of sulfadiazine for five to six days after the temperature reaches normal

During the course of sulfadiazine therapy the urine of the patient should be kept alkaline by adequate doses of *sodium bicarbonate* This is a new and important phase of sulfadiazine therapy It has been shown that

In recent years, *oxygen tents* have been greatly improved The canopy has been increased in size and is now obtainable in transparent pliofilm which adds greatly to the comfort of the patient and also permits the physician and nurse to have a clear view of the interior of the tent

High concentrations of oxygen from 50 to 100 per cent may be administered by either the B L B or the O E M meter *mask* In the former a small rubber bag serves as a rebreathing bag and sponge rubber discs are employed as combination inspiratory and expiratory valves This mask is best employed with high flows of oxygen in order to overcome the resistance created by the sponge rubber disc and to prevent excessive accumulation of carbon dioxide which would otherwise be found in flows of oxygen from 3 to 4 liters per minute In the meter mask an injector is used which mixes oxygen with air before entrance to the mask and *supplies in an accurate way the prescribed* concentration of oxygen (40 to 100 per cent) in the inspired air No rebreathing occurs with the meter mask since a delicate inspiratory valve is placed in front of the latex bag which serves as a collecting container for the inspired oxygen The minimal resistance in this mask makes it possible to use it with low flows of oxygen Low oxygen flows from 3 to 4 liters per minute may be employed in this mask to yield concentrations of 40 and 50 per cent oxygen without accumulation of carbon dioxide Although mask oxygen therapy may be effectively employed in many patients with pneumonia there are others in whom continuous appliance to the face is followed by discomfort Under these circumstances the administration of oxygen could be continued with an oxygen tent if it is available or with a nasal catheter The special advantages of either the B L B or meter mask are that very high oxygen concentrations from 50 to 100 per cent may be administered when indications for it are present such as peripheral circulatory shock or edema of the lungs

In certain severe cases of pneumonia that are complicated by pulmonary edema the oxygen mask metered for positive water pressure may be indicated In treating pulmonary edema it is customary to begin with high pressures such as 4 cm , and gradually *lower the pressure to 2 and 1 cm* of water From 40 to 100 per cent oxygen is employed The combination of helium and oxygen is also used in the treatment of certain cases of pulmonary edema For this the helium oxygen hood is employed at first with a relatively high pressure of from 5 to 6 cm. of water then with pressures gradually reduced to 1 cm and finally to atmospheric pressure

Stimulation —The circulation of the patient must be watched for the first indication of failure *Heart failure per se* is much less common in pneumonia than has been supposed In a majority of fatal cases death is referable to either respiratory failure or vasomotor paralysis The latter is indicated by a low blood pressure, rapid thready pulse profuse perspiration and other symptoms of shock This is best treated with epinephrine, in doses of 0.5 to 1 cc which may *be given every twenty minutes for 6 doses* or until the blood pressure and pulse improve Caffeine may be used instead of epinephrine, or may be alternated with it Alcohol as a stimulant still has its advocates but the consensus seems to be that it should be administered only to patients who are chronic alcohol addicts Intravenous glucose or glucose and saline solutions have been used in recent years to produce an elevation of the blood pressure Care should be taken however not to overtax the right side of the heart by giving too much fluid by vein as *in some instances a rapidly progressive* pulmonary congestion and edema result In the hands of the writer this method of stimulation has been disappointing It is no longer considered good practice to administer digitalis as a routine in the treatment of pneumonia This drug is indicated only in cases which show definite signs of heart failure or for those patients who develop auricular fibrillation

Sulfonamide Therapy —The discovery of the sulfonamide drugs marks a revolution in the treatment of pneumococcal pneumonia The first of these drugs was sulfapyridine a derivative of sulfanilamide which differs from that drug in that one hydrogen atom of the sulfanilamide group is replaced by a basic pyridine group The first report on the therapeutic value of sulfapyridine was made

ministration Sodium sulfadiazine should be administered only by the intravenous route The drug is quite alkaline and necrosis may result if some of the fluid escapes into the subcutaneous tissue Usually 5 Gm in 100 cc of distilled water is given for an initial dose to the average adult When this dose is injected into the vein a free sulfadiazine level of 5 to 10 mg per 100 cc of blood is immediately established In order to maintain this effective level oral therapy with sulfadiazine should be started immediately after the intravenous injection If for various reasons oral therapy is not possible maintenance requirements must be provided by additional intravenous injections of sodium sulfadiazine In such case 2 Gm every eight hours is sufficient

The effect of sulfadiazine on the clinical course of pneumonia is usually prompt and dramatic Within a comparatively few hours after the initial dose the temperature may drop to normal by crisis and the patient seems much more comfortable With the drop in temperature there is a corresponding fall in pulse and respiration The drug however should not be discontinued at this point otherwise a relapse may follow As stated above the dosage may be cut to one half the previous amount and continued at four hour intervals for twenty four to seventy two hours after normal temperature and pulse rate have been obtained Administration of sulfadiazine by rectum has been tried in patients who cannot tolerate the drug by mouth but absorption by this route is slow and the clinical results are unsatisfactory

The Toxic Effects of Sulfonamides—The toxic effects of sulfonamides are varied Sulfathiazole and sulfadiazine are both less toxic than sulfapyridine However all three of these drugs can produce serious and even fatal reactions The patient must therefore be closely watched for toxic manifestations while sulfonamide therapy is being administered Similar toxic manifestations occur with all three drugs but are observed less frequently with sulfadiazine than with either sulfapyridine or sulfathiazole

The TOXIC SYMPTOMS which may follow the use of sulfadiazine are as follows NAUSEA and VOMITING are rarely seen so rarely that the question will usually be raised as to whether the symptoms are caused by the drug or by the infection

LEUKOPENIA is also a rare occurrence The leukopenia which exists before sulfadiazine is started is not a contraindication to its use When leukopenia develops during the course of treatment however it is usually wise to discontinue the drug at once A few cases of true agranulocytosis and several cases of purpura hemorrhagica have been reported

ANEMIA AND HEPATITIS—The severe hemolytic anemia which was seen occasionally during the use of sulfanilamide and sulfapyridine has been rarely observed with sulfathiazole or sulfadiazine Toxic jaundice is occasionally encountered

DRUG FEVER is often accompanied by dermatitis and occasionally by episcleritis The temperature is usually of low grade and subsides quickly after the drug is withdrawn The rash may be maculopapular scarlatiniform or morbilliform

NERVOUS and MENTAL MANIFESTATIONS occasionally psychoses have been reported following use of the sulfonamides This was more noticeable with sulfapyridine than it has been with sulfathiazole or sulfadiazine The symptoms most frequently reported have been marked mental depression delirium and disorientation Occasional instances of peripheral neuritis have been observed

COMPLICATIONS IN THE URINARY TRACT—Renal complications are the most frequent of the untoward manifestations of sulfadiazine therapy There is every reason to believe however that the urinary complications can be largely avoided by the forcing of fluids and the alkalinization of the urine The crystals of sulfathiazole and sulfadiazine are frequently found in the urine of patients who are receiving these drugs Usually they cause no unpleasant symptoms As a rule the crystals appear only after the urine has been allowed to stand at room temperature for several hours Macroscopic hematuria occurs in 1 to 2 per cent of patients Hematuria is nearly always associated with crystalluria Hematuria may or may not be accompanied by sharp pains in the costovertebral angles When because of insufficient fluid intake large quantities of crystals are precipitated in the tubules or around

the solubility of sulfadiazine is greatly increased in the alkaline urine and because of this fact *crystalluria* and the dangerous sequelae which often result from it can be avoided by maintaining the urine at a *p*H of at least 7.5

Gilligan Garb and Plummer advise 6 Gm (90 grains) of sodium bicarbonate as an initial dose to be administered by mouth with the first dose of sulfadiazine This should be followed by 2 6 Gm (40 grains) of the alkali every four hours with each Gm of sulfadiazine The total twenty four hour dose of bicarbonate would therefore be 15 6 Gm The alkali therapy should be continued for twenty four hours following cessation of sulfadiazine therapy

As the incidence of crystalluria is particularly high when sodium sulfadiazine is administered intravenously sodium lactate by vein should be given if the patient is unable to take alkali by mouth Sodium lactate or sodium citrate by mouth may be preferred by some patients in whom sodium bicarbonate causes nausea or other unpleasant symptoms The oral dosage of sodium lactate is one third greater, and that of sodium citrate one fifth greater than that of sodium bicarbonate The daily urinary volume of patients on sulfadiazine therapy should be 1500 to 2500 cc

If the patient does not react favorably to sulfadiazine, the blood should immediately be tested for its sulfadiazine level If this is very low steps should immediatel be taken to increase the blood concentratio either by increasing the amount of sulfadiazine by mouth or by giving sodium sulfadiazine intravenously

Sodium sulfadiazine (or sodium sulfathiazole) is a soluble form of the drug which i intended for emergency intravenous use It is available either as a white powder or in a 20 per cent aqueous solution It is readily soluble in distilled water and should be well diluted preferably to 5 per cent before ad

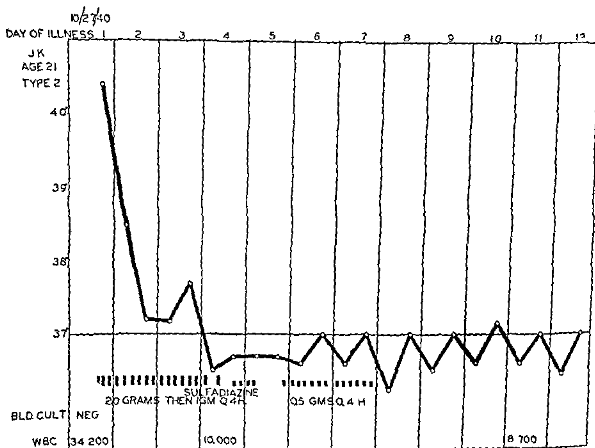


Fig 16—Temperature chart of a patient with Type II pneumonia treated with sulfadiazine during the first twenty four hours of his illness Initial dose 2 Gm., then 1 Gm every four hours until the temperature reached normal (Courtesy of Dr Norman Plummer)

of the disease In many instances a rapid drop of temperature occurs shortly after the injection and is accompanied by a corresponding drop in the pulse and respiration rate Cecil and Blake showed that monkeys affected with fatal Type I pneumonia could in every instance be saved by the intravenous injection of Type I antipneumococcus serum In these experiments the serum not only lowered the temperature but quickly cleared the blood of pneumococci

In recent years antipneumococcus serum has been gradually refined and concentrated so that the modern product is many times more potent than the original Furthermore because of the reduced protein content the refined serum is much less prone to cause reactions in the patient

The following table compiled from various sources gives the results of serum therapy for the more prevalent types of pneumonia

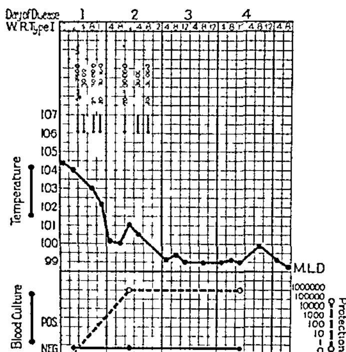


Fig 17.—Pneumococcus Type I pneumonia. Treatment with Type I concentrated serum on the first and second days of the disease The broken line below indicates the appearance of immune bodies in the patient's blood after the injection of serum

Fatality Rates for Pneumococcus Pneumonia of the Commoner Types, with and without Serum

Type	*Serum Treated*			*No Serum*		
	Cases	*Deaths*	*Per cent*	*Cases*	*Deaths*	*Per cent*
I	3136	429	13 6	558	182	32 6
II	964	302	31.3	967	424	43.8
IV	139	35	25 1	516	187	36.2
VII	109	13	11 9	404	117	28.9
VIII	41	4	9.8	319	60	18.8
XIV	39	4	10 2	167	34	20.3
Total	4428	787	17 7	*2931	1004	34.2

The one exception to these satisfactory results with serum has been in the case of Type III pneumonia in which Type III antipneumococcus serum has yielded rather disappointing results

It will be seen from these figures that the death rate is cut approximately one half by serum therapy The reduction however is more marked when only patients treated early are included

the calices concretions and actual calculi may form in the pelves of the kidney These may produce gross hematuria and sharp pain in the costovertebral angles, and if a stone or gravel engages the ureter, typical renal colic may ensue Sharp increase in the level of nonprotein nitrogen of the blood has been noted in a small percentage of cases Occasionally when crystalluria is marked there may be a pronounced reduction in the urinary output or even complete urinary suppression In such cases the urine becomes very scanty and of a smoky appearance, and contains large numbers of crystals and red blood cells A number of fatalities have been reported in such cases The urinary complications described above can be avoided by careful supervision of sulfonamide therapy Fluids should always be forced to amounts of 3 or 4 liters daily, and if oliguria develops the fluid intake should be increased promptly, and the drug discontinued If there is marked or complete suppression of the urine, particularly when accompanied by ureteral pain fluids should be forced by mouth and parenterally and ureteral catheterization should be employed early if a fatal outcome is to be avoided

Recent studies have indicated that if the alkalinity of the urine is maintained by administration of adequate amounts of alkali precipitation of sulfonamide crystals does not take place in the urinary tract This is an important contribution to sulfonamide therapy and should go far toward eliminating serious urinary complications

Because of the occasional development of blood and renal complications every patient who is receiving sulfonamide therapy should have a routine blood count and urinalysis every forty eight hours during the period of drug administration

Two new sulfonamide derivatives have recently been introduced by English investigators sulfamethazine and sulfamerizine Both products apparently possess bacteriostatic power over the pneumococcus and streptococcus similar to that observed in the case of sulfathiazole and sulfadiazine At the present time therapeutic investigation of these new drugs is being conducted in several American hospitals However they have not yet received sufficient study to justify their use in practice

Acquired Hypersensitivity to Sulfonamides —Bullowa and others have reported instances of acquired hypersensitivity to the various sulfonamides where they have been administered repeatedly to the same patient Two such cases have come under the observation of the writer In such patients the first administration of the drug has caused no unpleasant symptoms In some cases this sensitization to one of the sulfonamides holds also for its closely related derivatives Hypersensitivity to sulfonamides manifests itself by the prompt appearance of fever skin rash and systemic reactions The rash is morbilliform or urticarial and is occasionally accompanied by swellings of an angioneurotic character The rash is characterized by intense itching

Serum Therapy—Before the advent of sulfonamides, the only specific treatment for pneumonia was serum therapy After many years of experimentation the serum therapy of pneumonia had been developed to a point of efficiency where it was capable when properly used of cutting the death rate for the various types to approximately half that for untreated cases Within a year however after the introduction of sulfonamide therapy it became apparent that sulfonamide therapy was much simpler and more effective than serum therapy Serum therapy is still used in certain selected cases A brief discussion therefore of serum therapy seems desirable

Antipneumococcus serum was first prepared against pneumococcus Type I pneumonia by immunizing horses against Type I cultures and using their serum intravenously in patients with Type I pneumonia The first reports on the value of Type I serum were made by Cole and his co workers at the Rockefeller Institute In a series of 431 cases the fatality rate was 10 2 per cent as compared with the usual rate of 30 per cent for cases not receiving serum Since the original studies of Cole the value of Type I serum has been widely corroborated in all parts of the world and in recent years specific serums have been introduced for the other types of pneumonia

The clinical effect of specific serum on a patient with pneumococcus pneumonia is often dramatic particularly if administered in the first twenty four to forty eight hours

102° F and often there is pain and swelling in various joints These symptoms persist for a few days and then disappear

Contraindications to Serum Therapy —Serum therapy is contraindicated (1) in all cases of pneumonia where the type of pneumococcus cannot be determined (2) in patients who give a history of recent administration of serum (3) in severe asthmatics who are not considered good risks for serum therapy, (4) in the presence of a strongly positive skin or eye reaction to horse or rabbit serum.

Combined Sulfonamide and Serum Therapy—There has been considerable debate in the recent literature concerning the advisability of combining sulfonamide therapy with serum therapy in the presence of severe pneumonia *All are agreed that in the average* case sulfonamide therapy suffices However a certain number of pneumonia patients die in spite of sulfonamide therapy and it has been claimed that a percentage of these patients could be saved by a combination of serum with chemotherapy Plummer and his associates have recently published an extensive statistical study in which they conclude from carefully controlled figures that the fatality rate was not affected by the addition of serum to chemotherapy A final answer can not be given to this question at the present time In any case the present role of serum in pneumonia appears to be its use in the treatment of patients who cannot tolerate sulfonamides or who do not respond satisfactorily within twenty four to forty-eight hours to sulfonamide therapy Since the introduction of sulfonamides there has been a rapid and progressive fall each year in the amount of serum administered in both hospital and private practice

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STREPTOCOCCUS HAEMOLYTICUS PNEUMONIA

Definition —*Streptococcus haemolyticus* pneumonia is usually classifiable as broncho pneumonia though at times it takes on the picture of lobar consolidation

Incidence —The *hemolytic streptococcus*

It should be stressed that serum therapy is highly specific for type and therefore requires careful bacteriologic control Serum should always be given intravenously and in adequate doses In most cases an uncomplicated pneumonia in a person twenty five to thirty years of age responds with rapid crisis to the introduction of 50 000 to 100-000 units of serum These doses are probably sufficient for types other than Type II, which generally requires 100 000 to 200 000 units for uncomplicated cases The required dosage increases with age with delay in treatment in patients who are pregnant or whose blood cultures reveal a bacteremia and in those cases with extensive involvement In the last few years antipneumococcus rabbit serum has been introduced as a substitute for horse serum over which it has certain theoretical and practical advantages

The patient is first questioned as to previous injections of horse or rabbit serum as well as to a history of hay fever asthma or other allergic phenomena Conjunctival and skin tests are next made with a 1 10 dilution of serum and if after fifteen minutes these tests are negative 1 0 cc of serum is slowly injected intravenously The patient should be carefully watched for increase of dyspnea cyanosis flushing of the face and for the appearance of urticaria If any of the signs of a reaction occur the needle should be withdrawn immediately and 0 5 cc of epinephrine injected subcutaneously Epinephrine may be repeated two or three times if the reaction increases After the first injection of serum there is very little danger of reaction so that larger amounts can be safely administered A second injection of 15 to 20 cc is given intravenously from one to two hours later and this dose is repeated every two or three hours until the patient has received about 100 000 units of serum The amount of serum administered on the following day is determined by the clinical condition of the patient If as often happens the patient s temperature drops to normal no further serum therapy may be necessary If on the other hand the patient s condition is worse or if it remains unchanged intensive treatment is continued On the third day the same policy is pursued It has been found that if any benefit is to result from serum treatment it is usually apparent after two or three days of treatment

At the present time there is a tendency in some institutions to give the entire therapeutic dose of serum in one injection This may be achieved by direct intravenous injection of serum with a large Luer syringe or better still by making use of an intravenous infusion set diluting the serum with 500 cc of sterile physiologic salt solution and allowing the mixture to enter the vein very slowly by gravity This method of administering serum probably gives a more brilliant therapeutic effect but should be employed only by those thoroughly familiar with serum therapy In ordinary circumstances it would seem safer to divide the therapeutic dose into two or three injections of 25 000 to 50 000 units each

SERUM REACTIONS —The injection of serum may be followed by several types of reactions (1) the allergic reaction, (2) the thermal reaction, (3) serum sickness

(1) *The Allergic Reaction* —When individuals are highly sensitive to horse or rabbit serum symptoms of shock may appear a few minutes after the introduction of serum The patient suddenly becomes dyspneic, there is flushing of the face and asthmatic breathing followed by sweating urticaria and general anxiety The symptoms can usually be relieved by the prompt hypodermic injection of 0 5 to 1 cc of epinephrine 1 1000 solution Shocks of this kind may end fatally but this seldom happens except in cases where proper precautions have not been taken

(2) *Thermal Reaction* —Sometimes the injection of antipneumococcus serum is followed by a foreign protein reaction which is quite different in character from the allergic one Thirty to sixty minutes after the injection of serum the patient has a chill which is followed by a rapid rise in temperature The temperature remains high for several hours then there is a rapid drop accompanied by profuse perspiration

(3) *Serum Sickness* —The severity of serum sickness depends in part on the amount of serum protein injected Symptoms usually appear seven to fourteen days after the injection of serum though they may come earlier The patient breaks out in a profuse urticaria the temperature rises to 101° or

not reduce the incidence of empyema Cases that develop empyema usually require surgical intervention and thoracotomy, though a certain number will recover following multiple aspirations of the chest In the last war it was found that better results were obtained when thoracotomy was postponed until the pleural fluid took on a frankly purulent quality Antistreptococcus serum has been advocated but is less efficient than sulfonamide therapy

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STAPHYLOCOCCUS AUREUS PNEUMONIA

Staphylococcus aureus pneumonia is a comparatively rare form of pulmonary infection constituting about 1 per cent of all cases of pneumonia It is characterized by the bronchial type of consolidation suppurative bronchiolitis and multiple miliary abscesses A more complete description of *Staphylococcus aureus* pneumonia will be found in the chapter on *Staphylococcus aureus* Infections (p 164)

RUSSELL L CECIL

FRIEDLÄNDER S BACILLUS PNEUMONIA

At least 1 to 3 per cent of all cases of pneumonia are caused by the Friedlander s bacillus This micro-organism produces a characteristic lobar type of consolidation For a full description of Friedlander s bacillus pneumonia see Chapter on Friedlander s Bacillus Infections (p 314)

RUSSELL L CECIL

HEMOPHILUS INFLUENZAE PNEUMONIA

Hemophilus influenzae pneumonia is quite rare except in times of epidemics though the *H influenzae* is frequently found in association with other pathogenic organisms In such mixed infections the role of the *H influenzae* is difficult to determine though it probably enhances the virulence of the pneumococcus or streptococcus which accompanies it

Blake and Cecil produced experimental pneumonia in monkeys with pure cultures of *H influenzae* The characteristic features were a tracheobronchitis hemorrhagic edema of the lungs bronchiolitis and bronchopneumonia In man the pathologic changes are quite similar to those produced in monkeys There is a widespread injury to the mucosa and submucosa of the bronchi extending down into the bronchioles Its intensity may vary from a catarrhal inflammation to actual necrosis and destruction of the bronchial walls leading to acute bronchiectasis

The fatality rate of pure *H influenzae* pneumonia is difficult to determine because of its rarity and also because of the possibility that the infection was initiated by some other organisms or by a filtrable virus with the subsequent development of *H influenzae* pneumonia

The treatment of *H influenzae* pneumonia is symptomatic A few cases appear to have been favorably influenced by sulfonamide therapy but in others the use of the drug has been disappointing

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VIRUS PNEUMONIAS

During the past few years an atypical form of pneumonia of unknown etiology has been reported with increasing frequency No pathogenic bacteria have been found in the sputum or in the bloodstream of these patients Even in those cases that come to autopsy no bacteria have been recovered from the consolidated lung tissue This type of pneumonia has been generally referred to as virus pneumonia However as these

is responsible for 3 to 5 per cent of all cases of pneumonia, though its frequency varies from time to time depending on predisposing factors and the presence of epidemics of respiratory infection which create favorable conditions for invasion of the organism

Epidemics of streptococcal pneumonia have occurred at various times particularly during great wars In times of peace, streptococcal pneumonia is much less fatal than in times of war, except in those cases where local epidemics occur

Etiology —Streptococcal pneumonia occurs most frequently during epidemics of *influenza* or *of measles* Less frequently streptococcal pneumonia is secondary to a common cold, streptococcal sore throat, scarlet fever or erysipelas Occasionally it acts as a secondary invader in pneumococcal pneumonia At other times however particularly in epidemics when the virulence of the organism is greatly increased streptococcal infection of the lungs may be primary, that is without any preceding illness

Morbid Anatomy —In the vast majority of cases the *Streptococcus haemolyticus* produces a pneumonia of the bronchial or lobular type The characteristic lesion varies from an interstitial pneumonia with peribronchial nodes to more extensive lobular consolidations with subpleural abscesses and interstitial suppurative pneumonia In monkeys with experimental pneumonia Blake and Cecil were able to duplicate these lesions and showed that the larger doses of organisms produced a more extensive lobular consolidation and tissue necrosis As in pneumococcal pneumonia the lower lobes on one or both sides are the ones most frequently involved

Symptoms and Signs —The symptoms vary with the severity of the infection The sporadic cases are prone to be mild with symptoms quite similar to those of pneumococcal bronchopneumonia The onset is usually gradual and follows influenza measles or some other preceding infection The temperature curve is of the irregular type and the signs in the chest are indefinite In the majority of cases small areas of dulness and moist rales comprise the positive physical findings

In epidemics of streptococcal pneumonia such as that which occurred during World War I, the clinical course takes on a more malignant character At such times the disease may be primary without any preceding infection The leading symptoms are severe intoxication the remittent type of fever cough with mucopurulent or bloody expectoration intense dyspnea and cyanosis and a tendency to early infection of the pleural cavity, with the development of empyema Pleural effusion is sometimes present within twenty four hours of the time of onset The pleural fluid is at first bloodstained and contains innumerable streptococci later it becomes frankly purulent The intrapulmonary process is frequently obscured by the effusion and the physical signs may be not unlike those of pneumococcal pneumonia the fluid transmitting the bronchial breathing quite distinctly The pneumonia is septic in type, especially in those cases in which streptococci invade the bloodstream and not infrequently results in the formation of pulmonary abscess Recovery is slow, with convalescence long drawn out, especially when the disease is complicated by empyema

Diagnosis —The diagnosis of streptococcal pneumonia is made from the examination of sputum The character of the pneumonia can be determined by x ray examination It is particularly important in following this type of pneumonia, to be on the lookout for empyema

Prognosis —In endemic cases the prognosis is excellent Lawrence and Sutliff found in analyzing a group of 81 cases that there were 10 deaths with a fatality rate of 12 3 per cent In a series recently reported by Keefer and his associates the death rate was 18 per cent These figures are in sharp contrast to those obtained in the epidemic of 1917–1918 when the fatality rate of epidemic streptococcal pneumonia ran as high as 50 to 60 per cent At the present time, of course the prognosis has been greatly improved by the introduction of sulfonamide therapy

Treatment —The treatment of streptococcal pneumonia differs in no essential respect from that of pneumococcal pneumonia Sulfonamide therapy is of great value particularly in those cases where it is administered early in the disease According to Keefer however sulfonamide therapy does

lent in various parts of the United States The onset was acute with headache chilly sensations, malaise and coryza Several patients developed a hacking cough which in a few cases was accompanied by tenacious white mucoid sputum Physical signs were quite meager, consisting chiefly of small areas of dulness and a few moist rales The pneumonia was best demonstrated by x rays which showed soft infiltrating lesions either single or multiple and tending to be patchy Since the epidemic of American Q fever in 1940 several other cases have been reported Only one of the fifteen cases in the Washington epidemic died

Primary Atypical (Virus) Pneumonia of Unknown Etiology —During the last two or three years there has been prevalent a peculiar form of bronchopneumonia usually referred to as virus pneumonia It differs from the virus pneumonia caused by known viruses in that no etiologic agent of any kind has as yet been recovered from the infected patient

Incidence —Virus pneumonia has been reported from all parts of the United States and England The disease occurs sporadically and in small outbursts The incidence in a report from Cornell University was approximately nine per one thousand students The vast majority of reported cases of virus pneumonia have occurred in adolescents and young adults in schools colleges and army camps The seasonal distribution is variable and sporadic Cases may occur at any season of the year

Etiology —The term virus pneumonia has been applied to this group of cases in a rather unscientific way as no virus has as yet been actually isolated The only justification for the use of the term is the absence of pathogenic bacteria from the sputum In all probability primary atypical virus pneumonia is not a disease but a syndrome which may be caused by a number of different agents In the absence of the usual pathogenic bacteria from the sputum and blood it seems most likely that a virus is responsible for most of them Pneumococci of the higher types have been found in a considerable number of the cases and to a less extent hemolytic staphylococci and streptococci may be demonstrable in certain instances However the clinical course the x ray findings and the failure of these patients to respond to sulfonamide therapy would indicate that these occasional pathogenic bacteria were probably accidental inhabitants and not actively concerned with the infection

Epidemiology —Virus pneumonia may be either epidemic or endemic in its manifestation However none of the epidemics have been very extensive or comparable to those of influenza Apparently the disease can be transmitted by contact but it is not highly contagious The high incidence of virus pneumonia in nurses and doctors suggests that the disease is often contracted by contact

Morbid Anatomy —Because of the low fatality rate, the morbid anatomy of virus pneumonia has not received thorough study However, in the few cases which have come to autopsy, the lungs have presented the picture of a patchy, hemorrhagic, interstitial bronchopneumonia accompanied by acute bronchitis and bronchiolitis The gross picture reveals small areas of consolidation which in places become confluent the bronchi are filled with mucoid or purulent exudate The picture is not unlike that of the influenzal pneumonia which was so prevalent during World War I Microscopically the alveolar septa show thickening and infiltration with mononuclear cells The process is most marked in the alveoli surrounding the bronchioles The walls of the bronchi and bronchioles show necrosis and infiltration with polymorphonuclear leukocytes and their lumens are filled with an acute inflammatory exudate Many of the alveoli contain edematous fluid and red blood cells

Symptoms —The incubation period is not known but apparently may be from one to twenty one days The infection makes its appearance with fever malaise headache chilliness and cough The temperature ranges from 99° to 105° F but is usually between 100° and 103° F The cough is one of the most characteristic and distressing features of the disease It is dry and occurs in paroxysms which are sometimes extremely difficult to control Substernal soreness and tenderness of the abdominal muscles often result from the continuous coughing As the disease progresses the cough may become produc

cases have been more carefully studied by bacteriologists it has become clear that they are not all caused by the same virus Finland and Dingle have recently reviewed the subject of virus pneumonia and they divide these infections into two main groups (1) pneumonias associated with known nonbacterial agents (2) primary atypical pneumonias of unknown etiology

Pneumonias Associated with Specific Viruses—Several of these are worthy of special mention

Influenzal Pneumonia—It is now generally accepted that a filtrable virus, probably identical with that demonstrated by Smith, Andrews and Laidlaw has been the exciting agent in most of the widespread epidemics of influenza that have occurred in the last few years This virus is referred to as Influenza A virus Another virus known as Influenza B virus can give rise to the same picture, and there is indirect evidence that still other varieties of influenza virus can produce the characteristic clinical picture of influenza While many cases of influenzal pneumonia appear to be caused by secondary pathogenic invaders there is considerable evidence that some cases of simple and apparently uncomplicated influenza may extend down into the lungs and produce a pure virus pneumonia From studies made at the Boston City Hospital it appears that the influenza virus itself may set up a considerable bronchopulmonary reaction but that in most cases in human beings secondary infection with bacteria plays an important role and may alter the pathologic picture in the lungs

In the ferret and in the mouse the influenza virus may produce pulmonary lesions almost identical with those found in fatal cases in human beings From these animals no pathogenic bacteria can be cultivated from the lungs On the other hand in swine the influenza virus gives rise to a mild upper respiratory infection and pneumonia results in this animal only when the virus is accompanied by the swine influenza bacillus

In the case of human influenza it would appear that both the virulence of the influenza virus and the prevalence type and virulence of the secondary invaders determine the severity and the character of the complicating pneumonia

For further information concerning influenza and influenza pneumonia, refer to the chapter on Influenza (p 6)

Pneumonia Caused by the Virus of Psittacosis—Psittacosis, a disease of parrots is caused by a virus which when it invades the human being leads to a severe form of atypical pneumonia A description of this type of pneumonia will be found in the chapter on Psittacosis (p 49)

Pneumonia Caused by Rickettsial Infections (Q Fever)—For some time pulmonary lesions have been recognized as part of the clinical and pathologic picture of several rickettsial diseases notably typhus and Rocky Mountain spotted fever Perhaps the most interesting and important of this group is Q fever which has been observed in both Australia and America Australian Q fever was first reported in 1937 by Derrick, who coined the name "Q fever' from Queensland where the first cases occurred

The *clinical picture* of Q fever as described by Derrick is quite characteristic with acute onset of malaise, anorexia headache muscular pains drowsiness and fever Symptoms last from seven to twenty four days with recrudescence in some cases No mention is made of pulmonary involvement in Derrick s report The infectious agent was isolated by Derrick on guinea pig inoculation and typical rickettsia were demonstrable in the spleens of infected mice Derrick named the organism *Rickettsia burnetii* after Burnet who first isolated the agent It was found that the bandicoop a native rodent of the Australian bush was susceptible to Q fever and *Rickettsia burnetii* were obtained from naturally infected ticks collected from bandicoops

American Q fever first called 'Nine Mile fever' was described in 1935 by Davis and Cox An outbreak of pneumonia ascribed to the agent of Q fever occurred among the employees of the National Institute of Health in Washington D C in the spring of 1940 An agent recovered from a number of these patients proved to be a gram negative Rickettsia like organism that grew well in tissue cultures and was identified as the Rickettsia of Q fever The *clinical features* of the pneumonia which occurred in these cases were very similar to those of the virus of atypical pneumonias which had been preva

PNEUMONIA IN CHILDHOOD

Among the serious diseases of childhood pneumonia occupies a prominent place It is one of the most prevalent of the acute diseases seen in the children's wards of hospitals and is frequently attended by grave complications and sequelae Pneumonia in the child presents a disease entity similar to pneumonia in the adult but there are differences in onset course etiology and treatment which make it advisable to give pneumonia in childhood separate consideration

As in adult pneumonia, there are two bases upon which the disease is usually classified—etiology and pathology The etiologic classification is dependent upon the infecting organism pneumococcus streptococcus staphylococcus, etc This classification is assuming more and more significance because it gives a more accurate understanding of pneumonia and also supplies a basis for specific therapy The pathologic classification divides pneumonia into lobar bronchial and certain other less common forms This classification in the last analysis is dependent upon histologic studies so that there are bound to be many clinical discrepancies Recently and particularly since the advent of the x ray the clinical differentiation of these pathologic forms has become more accurate Because there is such a marked difference in the mortality rates of the lobar and bronchial varieties of the disease this classification is also of clinical significance Pneumonia in childhood may be primary or secondary The primary pneumonia is usually of the lobar form and the secondary of the bronchial variety

Etiology —In the majority of the cases of both lobar and bronchopneumonia in childhood the infecting organism is the pneumococcus In 1979 cases of childhood pneumonia studied bacteriologically by a number of different investigators the incidence of the various organisms was found to be as follows

Organism	Number of cases	Percentage of incidence
Pneumococcus Type I	275	13 8
Pneumococcus Type II	98	5.0
Pneumococcus Type III	73	3 7
Pneumococci of other types	1272	64.3
Organisms other than the pneumococcus	263	13.3
	1979	

The striking constrast to pneumonia in the adult is the much greater percentage of pneumococcus infections of the higher type In addition there is a higher incidence of streptococcus and staphylococcus pneumonia The following table compiled by Heffron shows the incidence of the more prevalent types of pneumococcal pneumonia in childhood

Pneumococcus type	Percentage distribution in 2745 cases
XVI	12.0
I	11.2
VI	7 7
XIX	3.9
V	3 6
IV	3 1
III	2 7
VII	2.1

It is evident that the incidence of types in the pneumococcal pneumonias of childhood is quite different from that of adults

Lobar Pneumonia —Formerly it was believed that almost all of the pneumonias in childhood were of the bronchial form This impression was obtained from statistical studies on autopsies and did not allow for the low death rate in lobar pneumonia and the much higher rate for bronchopneumonia Recently by the use of more accurate diagnostic methods particularly with the assistance of the x ray it has been shown that in children as in adults lobar pneumonia has a much higher incidence than bronchopneumonia In a series of 1270 cases of pneumonia at Bellevue Hospital 1012 or 79.3 per cent were of the lobar type

The histologic characteristics of lobar pneumonia are striking Lobar pneumonia presents primarily an exudative type of inflammation in which the alveoli are filled with leukocytes red cells and fibrin causing a more or less uniform consolidation usually of lobar or confluent lobular distribution The bronchi show a simple inflammation of the mucosa but no productive changes in the bronchial walls There is usually a septal lymphangitis and a pleuritis which may be dry or form an effusion of serum or pus

Bacteriologic studies of lobar pneumonia show the pneumococcus as the exciting organism in about 90 per cent of the cases Types I VI and XIV are the strains most frequently discovered

Lobar pneumonia usually succeeds an

tive, but this does not occur with the regularity of the cough in pneumoccal or streptococcal pneumonia In many cases the dry hacking cough persists throughout the illness The sputum is mucopurulent or blood streaked never rusty The malaise and muscular aching may persist throughout the course of the disease Transient sweats occur in some cases The writer recently saw a case which was accompanied by meningismus and stiff neck but these symptoms cleared up after forty eight hours

Physical Signs —Physical examination usually reveals little in the way of positive signs As a rule the patient does not appear to be seriously ill though there are exceptions to this rule The majority of the patients show little dyspnea or cyanosis The respiration and pulse rate may be normal or only moderately increased Auscultation reveals fine or medium moist rales occurring late in inspiration Occasionally definite areas of dulness can be demonstrated by percussion

Laboratory Findings —The leukocyte count is nearly always normal The sedimentation rate may be moderately elevated The urine reveals nothing noteworthy

X-ray Findings —Several writers have noted that the x ray findings are out of proportion to the physical findings Indeed the diagnosis of virus pneumonia has been made by x ray in more than one case in which nothing more than influenza was suspected In the majority of cases x ray shows increase in both hilar shadows with areas of inflammation extending outward toward the periphery of the lung field The lower lobes are most frequently involved and in the majority of cases both lower lobes are affected The areas of infiltration are softer than those of pneumococcal pneumonia

Course —The course of virus pneumonia is usually mild though the disease may take on a severe and even fatal course The impression is quite general that virus pneumonias run a longer course than the average pneumococcal or streptococcal infection However there are many exceptions to this rule Some patients continue to run a fever for several weeks The writer recently saw a typical case of virus pneumonia in a young woman which had been going on for eight weeks, and she was still running a remittent type of fever with definite signs at both bases

Prognosis —The prognosis of virus pneumonia is usually good The patients are generally adolescents or young adults who handle the infection well Accurate statistics as to the fatality rate are not yet available, but it certainly would not be above 5 to 10 per cent

Treatment —The treatment of atypical primary pneumonia is entirely symptomatic Codeine in ½ to 1 grain (0 03 to 0 06 Gm) doses may be necessary to control the cough Expectorants are sometimes helpful If these fail steam inhalations with tincture of benzoin may give some relief Transfusions have been recommended by several writers and certainly can do no harm Sulfonamide therapy has been tried without any significant effect Indeed some think that sulfonamides increase the discomfort of the patient It would seem logical however, to try sulfonamide treatment for at least forty eight hours on the chance that one is dealing not with a virus but with an undemonstrable pneumococcal or streptococcal infection

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cells which as the disease progresses produce a dense collar around the bronchi compressing and obstructing the lumina The bronchial mucosa shows a simple inflammation and the lumina become filled with a purulent secretion The air spaces around the involved bronchi are collapsed and distorted by pressure and while there is some infiltration with large mononuclear cells there is no exudate into the alveoli In bronchopneumonia the bronchi are compressed and frequently plugged with heavy purulent exudate and this in turn produces localized atelectasis and emphysema These changes are chiefly responsible for the irregular signs

Clinically bronchopneumonia is not a well defined entity The onset is indefinite and usually the extension from upper respiratory infection to bronchitis and bronchopneumonia is so gradual that it is impossible to say just when the latter does begin The temperature gradually rises but remains irregular and is usually not high The cough increases The secretions from the bronchi and upper respiratory tract become thick and purulent and are sometimes mixed with blood The respirations usually become rapid and may be painful As the toxemia increases there may be convulsions and frequently there are severe gastric and intestinal symptoms

The physical and *x ray findings* in the chest of a patient with bronchopneumonia are surprisingly few Occasionally even in an advanced case with marked toxemia physical signs are entirely normal The most constant physical finding is that of coarse rales either scattered throughout the chest or localized at the base of the lungs The x ray usually shows a generalized accentuation in the markings of the hilum and periphery In some cases generally late in the disease there are marked changes The x ray may show patchy or irregular areas of increased density representing either consolidated or collapsed lung or there may be the diffuse haziness of pleural involvement In such cases the physical examination reveals irregular areas of dulness impaired breath sounds and rales

The *diagnosis of bronchopneumonia* is made on the basis of a clinical course of severe respiratory symptoms and toxemia with the absence of localized chest signs such as are present in lobar pneumonia The temperature curve is characteristically irregular and of a spiking type The bronchial secretion differs from that in lobar pneumonia in being more profuse and of a more purulent nature The bacteriologic findings in bronchopneumonia are similar to those of lobar pneumonia but the incidence of the various organisms is different The bronchial form shows a higher frequency of streptococcus and staphylococcus infections and a correspondingly lower incidence of pneumococcus infections

The complications of bronchopneumonia are similar to those of the lobar disease The incidence of the various complications seems to depend more upon the etiologic organism than upon the pathologic form of the disease

Lipoid cell Pneumonia —In 1925 Laughlen described a type of pneumonia characterized by mononuclear cells containing fat globules so called foam cells which appear in the alveoli and alveolar walls In addition to this proliferative lesion there is a variable degree of polymorphonuclear infiltration and simple inflammation of the bronchial mucosa This condition designated as lipoid cell pneumonia is dependent upon the aspiration of oily substances The particular inflammatory reaction which follows varies with the kind of oil aspirated and with the microorganisms thus injected It is thought that the vegetable oils are the least irritating and animal fats the most so The lipoids most frequently implicated in these cases are milk fat liquid petrolatum cod liver oil and the medicated oils used in cases of infection of the upper respiratory tract

Lipoid cell pneumonia is seldom discovered previous to postmortem examination although there are a number of characteristics of the disease which should make it recognizable as a clinical entity The condition occurs in children usually in infants under two years of age who are debilitated and who give a history of having received some oily preparation over a considerable period of time The course may be acute or chronic In infants the failure to gain weight and the presence of a cough combined with rapid respirations but without dyspnea

upper respiratory infection In children the sudden rise in temperature is not as often accompanied by a chill as by vomiting or intestinal symptoms In very young children the onset is occasionally attended by convulsions With the high temperature the child is flushed and prostrated, the respirations are rapid and grunting and accompanied in most cases by a cough

As the *physical signs* in the chest are not pronounced early in the disease they are of little aid in making a diagnosis The first signs are those of slight dulness a slight diminution of the breath sounds and a few rales over the affected area The definite signs of consolidation do not appear until about the third or fourth day

The *chest roentgenogram* and *fluoroscopy* are of greater value than physical signs in diagnosing early lobar pneumonia Usually within twenty four to forty eight hours under the x ray a soft homogeneous shadow is seen over the involved lobe or area In the early stages of the disease there is an increase in the lung root markings and later a homogeneous shadow of increasing density usually extends from the root of the lung to the periphery In cases of involvement of the upper lobes the shadow is frequently triangular with the apex toward the hilum The x ray affords a clinical means of accurately differentiating between lobar pneumonia and the other pathologic varieties of pneumonia which either show no marked changes by x ray or present a picture characteristic of a different condition

The *early diagnosis* is based largely on the type of onset and the clinical course Any child showing respiratory symptoms and a high temperature should be suspected of having pneumonia An early clinical diagnosis is important in order that the infecting organism may be quickly determined and specific therapy instituted

Typing in the pneumonia of childhood is carried out in much the same way as in adults except that sputum is much less frequently obtained and hence the typing must be done on material secured either by the use of the laryngeal swab or by gastric aspiration In the swab method the posterior pharynx is irritated by the swab which initiates a cough and causes the patient to bring up a small amount of sputum or mucus This can then be used for typing by the Neufeld method Experience in a large series of cases has shown that by obtaining the material in such a way, typing can be completed almost as promptly as in the adult where sputum is available In addition to the bacteriologic studies of the bronchial secretions cultures of the blood pleural fluid spinal fluid pus from the middle ear and other localized processes should be carefully studied

The *complications* of lobar pneumonia in childhood are similar to those of the disease in adult life The most notable exception is purulent otitis media which in childhood is the most common occurring in about 15 per cent of the cases Empyema is the most frequent of the serious complications Meningitis pericarditis and endocarditis are rare complications, but when they occur they are usually fatal

The *prognosis* in lobar pneumonia is good Smith emphasizes the importance of making an accurate differentiation between lobar and bronchopneumonia because of the great difference in mortality rates of the two conditions and its consequent effect on prognosis His statistics showed a death rate of only 5.5 per cent in lobar as compared with a rate of 50 2 per cent in bronchopneumonia The mortality rate in both diseases is affected greatly by the age of the patient being very much higher in the first year of life

Bronchopneumonia —This form of pneumonia differs in many respects from the lobar type The clinical course is different It is a disease which occurs chiefly in infants and is usually secondary to bronchitis or one of the common contagious diseases of childhood It is very apt to follow an upper respiratory infection in a feeble or poorly nourished infant Clinically the incidence of bronchopneumonia is much lower than that of the lobar type In the 1276 cases of pneumonia studied at Bellevue Hospital only 264 or 20 7 per cent were bronchopneumonia

The *pathology of bronchopneumonia* is distinctly different from that of lobar pneumonia Whereas the primary feature of lobar pneumonia is an exudative inflammation which fully resolves bronchopneumonia is a productive inflammation The bronchial walls become infiltrated with mononuclear

cells which as the disease progresses, produce a dense collar around the bronchi compressing and obstructing the lumina The bronchial mucosa shows a simple inflammation and the lumina become filled with a purulent secretion The air spaces around the involved bronchi are collapsed and distorted by pressure and while there is some infiltration with large mononuclear cells there is no exudate into the alveoli In bronchopneumonia the bronchi are compressed and frequently plugged with heavy purulent exudate and this in turn produces localized atelectasis and emphysema These changes are chiefly responsible for the irregular signs

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should suggest lipoid pneumonia The physical and x ray signs are those of a diffuse bronchial or bronchopneumonic condition The bronchial secretion is sometimes characterized by the presence of mononuclear cells containing lipoid but this has not proved to be a reliable test In all cases of suspected lipoid cell pneumonia, tuberculosis should be ruled out by application of the tuberculin test and by studies of the bronchial secretions obtained either from aspirated gastric contents or from expectorated material

The prognosis in lipoid-cell pneumonia is variable and is dependent upon a number of factors the most important being the general condition of the child, its age, the kind of oil aspirated and the degree of concomitant infection Recovery from this type of pneumonia is by slow retrogression of the process

Treatment of the active condition is for the most part symptomatic and supportive Preventive therapy is highly important In the case of debilitated infants liquid petrolatum as a cathartic or in the form of medicated nose drops should be used only with caution When cod liver oil is not easily taken one of the concentrated vitamin preparations should be substituted

Treatment —The methods of therapy used in the pneumonia of childhood are similar to those employed when the disease occurs in adults It is important however, to emphasize a few points which apply particularly to the childhood type

In prophylactic treatment, the importance of giving careful attention to bronchitis and severe upper respiratory infection in the infant is stressed It has been pointed out that in private practice where there is more opportunity for preventive measures pneumonia is quite a rare disease while in general and city hospitals it is found to have a high incidence Various hygienic measures such as good nursing quiet and comfortable surroundings, and good ventilation are of great importance and should be adopted whenever possible The food should be mostly liquid and should not be forced Water should be allowed freely at all times

Cough, pain restlessness and gastro intestinal symptoms, such as nausea vomiting distention diarrhea and constipation must each be given careful attention Along the line of symptomatic therapy *oxygen administration* has been found to be of particular value It is a means of alleviating respiratory distress and lessening to a great extent the ill-effects of anoxemia Oxygen is more easily administered to children than to adults In the case of an infant a small tent functions as effectively as an elaborate oxygen chamber *Blood transfusions* are frequently used in the treatment of the pneumonia of childhood Protracted cases and especially those in which blood studies show a secondary anemia of variable degree respond best to this therapy

Serum treatment has been displaced almost entirely by sulfonamide therapy Now serum is indicated only in the occasional patient who cannot tolerate the sulfonamides or who does not respond to them

The sulfonamide drugs one after another have been tried in childhood pneumonia as in other infectious diseases Sulfanilamide has very little value Sulfapyridine is difficult to administer because of its toxic reactions At the present time the choice is between sulfathiazole and sulfadiazine the sodium salt of either to be used when parenteral administration is required The following dosage schedule is suggested

Age	1–3 mos	6 mos–1 yr	2 yrs	5 yrs	12 yrs
Oral Dosage	0 15 Gm every 4 hours	0 25 Gm (½ tablet) every 4 hours	0.25 Gm (½ tablet) every 3 hours	0.5 Gm (1 tablet) every 4 hours	1 0 Gm (2 tablets) every 4 hours
Parenteral Dosage	0.5 Gm every 8–12 hours	1 0 Gm every 8–12 hours	1.5 Gm every 8–12 hours	2 0 Gm every 8–12 hours	2.5 Gm every 8–12 hours

All of the sulfonamides may produce serious toxic reactions and none of the drugs should be used without full knowledge of and regard for the toxic manifestations

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STREPTOCOCCAL INFECTIONS

INTRODUCTION

STREPTOCOCCAL infections comprise a wide and varied group of clinical conditions It is probably not an exaggeration to state that streptococci are responsible for a greater variety of pathologic processes than any other group of bacterial agents Not only are they the direct cause of a large number of distinct diseases but owing to their wide distribution they are also important secondary invaders In addition streptococcal infections appear to initiate certain other disease processes the precise nature of which is not yet clearly understood

Classification of the Streptococci—In general streptococci are of three main varieties the *hemolytic* the *green producing* or the *viridans* and the *indifferent* The *hemolytic* streptococci constitute by far the most important of these varieties and are responsible for the great majority of streptococcal diseases The role of the *green producing* and *indifferent* varieties is largely confined to that of secondary invaders although in a certain number of conditions notably subacute bacterial endocarditis they are important primary agents

The importance of the *hemolytic* streptococci is such that they have become the subject of much intensive investigation and it is now known that there exist several distinct groups within the hemolytic variety itself The work of Lancefield which has been confirmed by numerous investigators is of particular significance in this connection Lancefield has shown by means of precipitation reactions that the *hemolytic* streptococci can be divided into distinct serologic groups, designated for convenience as Groups A B C D E F and G Of these Group A is by far the most important and accounts for an overwhelming majority of streptococcal diseases in man Thus it has been shown that practically all cases of scarlet fever acute tonsillitis erysipelas and puerperal sepsis are due to infection with Group A organisms Strains of this group may possess both toxin producing and invasive properties Strains belonging to Groups B to G are commonly found in a number of animal diseases as well as in a variety of sources in nature Such strains are also frequently found as harmless saprophytes in man but only in occasional cases are they responsible for clinical infection For example one of the natural habitats of Group D organisms is the human gastro intestinal tract but strains of this group are only occasionally pathogenic for man In a recent study Hare has further shown that only about one third of the strains of *hemolytic* streptococci found in the nose and throat of normal human beings belong to Group A The remaining two thirds of the strains belong to the essentially nonpathogenic groups B to G

The problem of classification is further complicated by the fact that there are a large number of distinct *types* within each of the various *groups* of *hemolytic* streptococci Thus Griffith has shown that there are at least 24 serologic types within Group A and probably others exist There is evidence that the distribution of these types varies in different localities and also in the same locality from time to time In general there is little indication that any particular types are more pathogenic than others but this phase of the problem requires further study While these facts reveal the complex nature of the *hemolytic* streptococci they make possible for the first time an intelligent approach to the study of the epidemiology of hemolytic streptococcal infections

Treatment—The introduction of *sulfanilamide* and its derivatives has revolutionized the treatment of hemolytic streptococcal infections Prior to what may justifiably be called the era of chemotherapy the only specific therapy available for these infections was antitoxic serum However the pathogenic action of hemolytic streptococci is in large measure due to their invasive capacity and no serum has been developed which inhibits this property Since the introduction of *sulfanilamide* and its derivatives the situation has been radically changed and there are now available highly specific chemotherapeutic agents for the treatment of hemolytic streptococcal diseases The various aspects of the treatment of individual diseases are considered in their appropriate places and it is only necessary to review certain general considerations

Sulfanilamide was originally introduced as a complex azo dye under the trade name prontosil It was soon discovered however, that prontosil owed its specific effect to a comparatively simple constituent para amino benzene sulfonamide By general agreement this substance has since become known by the term sulfanilamide A number of sulfanilamide derivatives have since been introduced which are equally effective therapeutically and exhibit less toxic properties The most satisfactory of these preparations are sulfathiazole and sulfadiazine

Sulfanilamide and its derivatives exert a remarkable chemotherapeutic effect in hemolytic streptococcal infections The precise mechanism of their action is not yet understood but it is generally agreed that they inhibit bacterial growth Sulfathiazole and sulfadiazine as well as sulfanilamide may be given by mouth and the dose recommended varies from 6 to 12 Gm (90–180 grains) daily in divided doses according to the severity of the infection Because of individual variations in absorption and excretion it is important that whenever possible the concentration of the drug in the blood should be determined frequently during the course of treatment If the drugs cannot be taken orally the sodium salts should be administered intravenously One of the untoward complications of sulfathiazole and sulfadiazine therapy is the deposition of the drugs in crystalline form in the renal tubules sometimes producing severe hematuria and occasionally renal shut down This complication can be avoided by administering bicarbonate of soda in equal amounts with the drug

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ACUTE TONSILLITIS

Definition—An acute infection of the lymphatic tissue in the region of the pharynx and nasopharynx occurring in both sporadic and epidemic form The most usual variety appears as an acute inflammation of the palatine or faucial tonsils but in nearly all cases the other lymphatic tissue in this region is also involved

Anatomy—The collection of lymphadenoid tissue at the entrance to the respiratory and alimentary passages is commonly referred to as Waldeyer s or the tonsillar ring It consists of three major and several minor aggregations of lymphatic tissue The larger masses are known as the pharyngeal tonsils (the adenoids) the palatine or faucial tonsils and the lingual tonsils The smaller collections are found around the orifices of the eustachian tubes between the faucial and the lingual tonsils and in scattered patches beneath the mucous membrane of the entire nasopharynx

Histologically the tonsils are composed of lymphatic tissue similar in structure to other lymphatic glands The lymphatics of the faucial and lingual tonsils drain into the anterior group of the deep cervical glands the most important of which the tonsillar gland is found just below the angle of the jaw The lymphatic drainage from the naso pharyngeal tonsils (adenoids) is by way of the posterior cervical glands which are situated along and under cover of the posterior border of the sternomastoid muscle

Age Incidence —Acute tonsillitis is particularly prone to occur during childhood and early adult life Infants appear to possess a considerable degree of immunity and the incidence diminishes in later adult life

Seasonal Incidence —In the United States and Canada infection of the tonsils occurs most frequently during the winter and spring months reaching a peak during the month of March It is often seen among residents of hospitals at this time of year and may constitute a minor epidemiologic problem

Sporadic and Epidemic Forms —While the sporadic form of the disease is extremely common it is often possible to trace the source of the infection to another recent case Epidemics are usually confined to small institutional communities but occasionally they assume widespread proportions In the latter event the infection is of a particularly virulent nature and is more usually termed epidemic sore throat'

Etiology —Under normal conditions the tonsils harbor within their crypts a wide variety of pathogenic bacteria It is difficult to say whether the sporadic form of the disease is the result of infection by these bacteria operating under peculiarly favorable conditions or by a new pathogen introduced from without Probably infection may occur by both of these methods In the epidemic form however there can be no doubt that the agent is exogenous in nature

Although a great variety of organisms may gain access to the tonsils the clinical entity *acute tonsillitis* is for all practical purposes a hemolytic streptococcal disease There seems no basis in fact for the statement found in the older books that a variety of other organisms such as streptococcus viridans pneumococcus and staphylococcus are occasionally responsible ' Further more recent investigations have shown that in an overwhelming majority of cases hemolytic streptococci of Group A are implicated

Pathology —The tonsils are greatly increased in size and markedly hyperemic The crypts are filled with an intense inflammatory exudate of soft cheesy material which *projects from the mouths of the crypts* It is composed of disintegrating polymorphonuclear leukocytes desquamated epithelium lymphocytes and bacterial debris In more severe cases the exudate is fibrinous in character Histologically the picture is that of an acute, exudative inflammatory process in lymphatic tissue but without specific features

Symptomatology —A typical attack is characterized by an abrupt onset with severe constitutional disturbances and an acute angina of the throat There may be a definite chill or chilly sensations and the temperature rises rapidly reaching 103° to 105° F in severe cases General malaise with aches and pains in the back and extremities *are almost invariably present The tonsils* are red and swollen with patches of foul smelling exudate protruding from the orifices of the crypts In particularly severe cases the exudate may form a false membrane over the surface of the tonsils The glands in the anterior cervical region become enlarged and tender Swallowing is attended by great pain The degree of general prostration may be quite out of proportion to the severity and extent of the local lesion The acute inflammation usually subsides within four or five days leaving the patient with nothing worse than a feeling of general weakness

The foregoing account is typical of an attack of moderate severity without complications or sequelae The intensity of the disease process however varies widely and may range from a superficial inflammation with little constitutional reaction to the most profound type of septic infection with complications and sequelae much more serious than the original condition

Complications —Peritonsillitis (quinsy sore throat) and acute otitis media are the most common complications An acute suppurative cervical adenitis may follow an unusually severe attack and in the virulent, epidemic type a variety of septic complica

tions may supervene The more remote sequelae will receive brief consideration in a later section

Diagnosis —The conditions which are most commonly confused with acute tonsillitis are *diphtheria* and *Vincent's angina* (ulceromembranous tonsillitis) In *diphtheria* the appearance of the throat is usually quite distinctive The exudate takes the form of a more or less uniform dull gray membrane which leaves a bleeding surface when removed In this disease the membrane also shows a tendency to spread over the pillars of the fauces and on to the uvula In tonsillitis the exudate is distributed in yellowish gray patches separated by red and inflamed tonsillar tissue These patches can usually be wiped away leaving the underlying tissue intact In all doubtful cases cultures should be made to determine the presence or absence of *Corynebacterium diphtheriae* *Vincent's angina* is usually a unilateral infection and is associated with a superficial necrosis and a dirty yellow exudate which leaves a bleeding surface when removed In this condition constitutional symptoms are slight or absent altogether but there is usually an enlarged and tender tonsillar gland Ulceromembranous tonsillitis is commonly associated with an ulcerative stomatitis foul breath and excessive salivation The diagnosis is confirmed by the demonstration of spirilliform and fusiform organisms It is often difficult to distinguish acute tonsillitis from the pharyngeal symptoms of *scarlet fever* The local symptoms are very similar and the differential diagnosis is dependent upon the presence of systemic manifestations peculiar to the latter disease An interesting and increasingly popular conception is that many cases of acute tonsillitis occurring in individuals who possess antitoxic immunity constitute in reality *scarlet fever sine eruptione*

Treatment —In the introductory section reference was made to the use of sulfanilamide sulfathiazole and sulfadiazine in the treatment of hemolytic streptococcal infections in general These drugs exert a remarkable effect on the course of tonsillitis but their indiscriminate use in all cases is not advised In the majority of instances the infection is comparatively mild and terminates spontaneously in a few days In the more severe type of case however the administration of one of these drugs is definitely indicated The dose recommended is from 6 to 8 Gm (90–120 grains) daily in four divided doses Untoward symptoms accompanying the use of sulfanilamide include nausea and vomiting dizziness and more rarely, cyanosis and pyrexia Sulfathiazole and sulfadiazine produce significantly fewer toxic reactions With these drugs it is wise to administer an equal quantity of bicarbonate of soda to prevent possible renal damage The following general measures are indicated in the treatment of acute tonsillitis The patient should be kept in bed and given large quantities of fluids until the acute attack is over The gastro intestinal tract should be properly regulated An ice bag should be provided for the neck and the mouth kept clean by the frequent use of a mouth wash The most effective local treatment consists in the application of hot irrigations directly to the surface of the inflamed tissues Either physiologic saline or a 2 per cent solution (1 teaspoonful to 1 quart) of sodium bicarbonate may be employed Symptomatic relief may be obtained by the use of acetylsalicylic acid (aspirin), Dover's powders or codeine

M H Dawson

SEPTIC SORE THROAT

(Septic Pharyngitis Epidemic Sore Throat)

Septic sore throat is a severe infectious disease which involves the tissues of the pharynx generally and which frequently occurs in epidemic form It will be recalled from the description of the anatomy of the tonsillar ring that the lymphatic tissue is widely distributed throughout the pharynx and the nasopharynx This is the tissue through which the infection enters and the resulting inflammation more or less diffusely involves the entire pharynx From the bacteriologic and pathologic points of view there is little justification for the separation of septic sore throat from acute tonsillitis For the clinician however the distinction serves a certain useful purpose and the term is usually employed to describe an acute tonsillitis of unusual severity which may have assumed epidemic proportions

Incidence —The disease occurs in both sporadic and epidemic forms The most striking examples of the latter variety have been due to milk borne infections in which the milk supply has been contaminated from human sources

Etiology —The hemolytic streptococcus is exclusively responsible for the production of this clinical syndrome It was formerly believed that a specific type of encapsulated organism the *Streptococcus epidemicus* was involved but more recent studies suggest that this organism is merely the mucoid variant of ordinary Group A hemolytic streptococci

Pathology.—The lesions first appear in the lymphoid tissue of the tonsillar ring and spread to involve the mucous membrane of the entire pharynx No distinctive features other than those of an acute fibrinopurulent exudate are present.

Symptomatology —The symptoms are essentially identical with those of the more acute form of follicular tonsillitis and it is often difficult or even impossible to distinguish between the two conditions

Complications —The complications of this condition are similar to those which occur in acute tonsillitis but they are apt to be more serious and of more frequent occurrence The infection may gain access to the blood stream or may spread downward to involve the tissues of the larynx and epiglottis In other cases deep cervical adenitis with suppuration may occur In a certain number of instances the infection travels via the lymphatic channels to the mediastinum and thence to the lining membranes of the heart and lungs

Diagnosis —The disease must be distinguished from diphtheria with which it is even more likely to be confused than is the ordinary acute tonsillitis In all suspicious cases the diagnosis should be confirmed by smear and culture

Treatment.—The treatment is the same as that of acute tonsillitis The administration of sulfanilamide sulfathiazole or sulfadiazine is indicated to prevent the development of complications or sepsis Since the introduction of chemotherapy the use of antistreptococcal serum has been abandoned

M H Dawson

PERITONSILLITIS

(*Peritonsillar Abscess, Quinsy Sore Throat*)

Peritonsillitis more commonly known as quinsy is an acute suppurative inflammation of the loose connective tissue between the capsule of the tonsil and its muscular bed Because of the anatomic relationships the collection of pus is usually confined to the upper two thirds of the tonsillar bed and the adjacent region of the palate In consequence the upper pole of the tonsil is pushed downward and medially the lower pole being more or less fixed in position by its attachment to the lateral wall In spite of the position and extent of a peritonsillar abscess the pus rarely extends down into the deeper tissues of the neck

Incidence —The disease shows a special predilection for young adults being relatively rare in children and in later adult life As is the case with other hemolytic streptococcal infections peritonsillar abscesses are more frequent in the late winter and early spring months

Etiology —Peritonsillar abscess may occur as a complication of simple tonsillitis but more frequently develops in those whose tonsils have been the site of repeated suppuration and cryptic retention The appearance of a tonsil in which an abscess is likely to develop is in no way distinctive The submerged type in which the openings of the crypts are hidden and obstructed is however frequently affected One attack confers no immunity but rather increases the susceptibility to subsequent attacks of the same nature *Streptococcus haemolyticus* is almost invariably the specific inciting agent

Symptomatology —The symptoms of peritonsillitis are similar to those of acute tonsillitis although as a rule the constitutional disturbances are less marked and there is not as much fever On the affected side the patient experiences great pain which often radiates to the ear Deglutition becomes painful and difficult the head is held rigidly and is often bent forward to the affected side The muscles of mastication are set to avoid movements of the jaw and there is copious secretion of tenacious saliva

The appearance of the throat is very characteristic On the involved side there is marked redness swelling and edema of the

palate and uvula and the tonsil is pushed downward and forward In a limited number of cases the process may be bilateral As the abscess increases in size the palate becomes more swollen and the uvula is pushed toward the opposite side In the majority of cases the center of the abscess occupies a position midway between the base of the uvula and the last upper molar tooth but occasionally the abscess points in other directions The duration of an untreated abscess varies considerably but it will usually rupture spontaneously in about a week's time

Complications —Complications of peritonsillar abscess are fortunately rare Edema of the glottis may occur In occasional cases the process may extend down into the deep cervical tissues producing thromboses and septic emboli

Treatment —The treatment consists in relieving the acute symptoms and evacuating the pus at the earliest possible moment Surgical interference is usually possible within thirty six or forty-eight hours and it is not necessary to wait for the development of fluctuation Sulfanilamide sulfathiazole and sulfadiazine may be ineffective in this condition because of the inhibitory action of large purulent exudates However these drugs may be administered in the hope that recovery will be hastened and complications prevented In the meantime the patient should be made as comfortable as possible It is often wise to administer morphine An ice bag should be provided for the neck and hot irrigations applied directly to the inflamed area at frequent intervals If possible fluids should be forced If they cannot be taken orally they should be given parenterally After evacuation of the pus hot saline irrigations should be continued to hasten resolution of the process Convalescence should not be hurried and every means should be taken to restore the patient's general health Particular attention should be paid to the urine in the following weeks for glomerular nephritis is a not infrequent sequela In order to prevent the occurrence of future attacks tonsillectomy is indicated This should not be done until a month or more after the subsidence of all acute symptoms Tonsillectomy when carefully and thoroughly performed almost invariably prevents subsequent attacks even in the most susceptible individuals

M H Dawson

ADENOIDS

Simple hypertrophy of the lymphatic structure of the pharynx is a more or less physiologic process during childhood but it frequently assumes pathologic proportions especially in the region of the pharyngeal tonsils and leads to the development of a characteristic clinical syndrome—adenoids

Pathology —Although the pharyngeal tonsils are subject to the same inflammatory processes which affect the palatine tonsils the most common pathologic change is one of simple hypertrophy The harmful effects of adenoids are in large measure due to the mechanical obstruction which they produce in the air passage and at the orifices of the eustachian tubes

Etiology —The exact cause of hypertrophy of the pharyngeal tonsils is not known The condition occurs most frequently between the fifth and tenth years and shows a tendency to involve more than one member of the same family It is said that the acute infections of childhood are apt to be followed by hypertrophy of this tissue but it is often difficult to determine which is cause and which is effect The same may be said of the relationship between repeated attacks of the common cold and adenoids Possibly a vicious circle is set up in which each condition in turn leads to the development of the other

Symptomatology —Adenoids produce a varied group of clinical symptoms of which mouth breathing is the most frequent and the most characteristic This is particularly noticeable at night and may be the cause of *snoring restless nights* and a feeling of suffocation The voice is thick and of a distinctive nasal quality difficulty is experienced in pronouncing certain consonants requiring nasal resonance Children with adenoids are especially prone to suffer from repeated attacks of upper respiratory infection—common colds sinusitis and recurring sore throats Owing to interference with drainage from the eustachian tubes acute and chronic infections of the middle ear are common

complications The only symptom may be slight deafness but examination frequently will reveal the presence of thickened and retracted membranes

The foregoing symptoms are those commonly associated with mild degrees of hypertrophy of the pharyngeal tonsils In more severe cases profound constitutional disturbances may result There may be definite retardation in both physical and mental development The face becomes lengthened the alae nasi collapsed and the upper lip shortened and retracted these changes together with the open mouth give the countenance an expression of stupidity so characteristic that it has been termed the *adenoid facies* Fortunately owing to the general education of the public improvement in hygienic conditions and routine examination of children of school age examples of this condition are becoming increasingly rare

Diagnosis —In well marked cases the diagnosis presents no difficulty In mild cases a history of recurring attacks of rhinitis with associated episodes of deafness with or without pain in the ears is most suggestive A most valuable sign in doubtful cases is the size of the lymphatic glands in the *posterior* cervical triangle just behind the border of the sternomastoid

Treatment —The only treatment consists in immediate and thorough removal by surgical methods The procedure is a very simple one and should be routinely performed when tonsillectomies are done for any reason The prognosis depends entirely upon the length of time for which the symptoms have persisted prior to operation

M H Dawson

CHRONIC TONSILLITIS

The term *chronic tonsillitis* as ordinarily employed is restricted to diseases of the palatine tonsils However it is only necessary to recall the anatomic distribution of the lymphatic tissue in the pharynx and nasopharynx in order to realize that inflammatory conditions are rarely confined to one portion of the tonsillar ring alone This is a most important point not only in relation to diseases of the tonsils themselves but also in regard to systemic diseases in which the tonsils may be considered to act as foci of infection Chronic tonsillitis includes conditions of both a hypertrophic and a chronic inflammatory nature

Chronic (Hypertrophic) Tonsillitis— At the outset it must be emphatically stated that enlarged tonsils are not necessarily diseased tonsils Some degree of hypertrophy of the lymphatic tissues of the pharynx is a physiologic process in children up to the age of puberty Such simple enlargement is not injurious to the individual unless it causes mechanical obstruction or unless it renders the patients susceptible to repeated attacks of sore throat However it is an exceedingly difficult problem to distinguish between physiologic and pathologic hypertrophy Excessive hypertrophy is of course readily recognized but there is a great middle ground where opinions vary widely In this connection it must also be kept in mind that hypertrophy of the tonsils is by no means synonymous with prominence of the tonsils Tonsils which are apparently small and buried may be actually quite as large as those which protrude more obviously into the oral cavity

Simple hypertrophied tonsils are enlarged pale in color and firm in consistency The symptoms for which they are responsible are essentially the same as those which have been described in the foregoing section on adenoids Treatment consists in surgical removal other procedures are not recommended

Chronic (Inflammatory) Tonsillitis— Chronic inflammatory tonsillitis is even more difficult to define than hypertrophy of the tonsils Some degree of inflammation is present within all tonsils and a distinction between that which is physiologic and that which is pathologic is almost impossible Practically all tonsils contain within their crypts considerable quantities of inflammatory exudate as well as a variety of pathogenic organisms The physician should therefore exercise great restraint before frightening his patients with unwarranted statements as to the condition of the tonsils

The term chronic inflammatory tonsillitis can justifiably be employed to describe that condition in which after an acute attack the tonsils remain enlarged

congested and edematous Such tonsils are highly susceptible to the development of subsequent attacks and are frequently the site of small abscesses Peritonsillar suppuration is a common complication After several attacks it is not unusual for the tonsils to shrink and atrophy leading to the development of the so called 'buried tonsil' In these cases the tonsils may be hard and fibrous but they frequently contain small suppurative foci

The foregoing type of chronic tonsillar infection will cause little confusion but there is a variety of other conditions in which the situation is much less clear The problem of chronic tonsillar infection as it affects the general health of the individual is an especially difficult one So too the relation between foci of infection in the tonsils and many systemic diseases is most perplexing In the majority of cases these relationships remain obscure even after the most careful and painstaking examination of the tonsils themselves The most innocent-looking tonsils particularly those of the small and buried type may harbor more infection than those which are large and prominent Furthermore definite infection of the tonsillar tissue may be present without leading to the development of any symptoms One of the most reliable signs of chronic tonsillar infection is the size and condition of the glands at the angle of the jaw Chronic enlargement of these glands with or without tenderness is probably a more valuable sign of chronic inflammation than either the history or the size and appearance of the tonsils themselves

M H DAWSON

TONSILLITIS IN RELATION TO SYSTEMIC DISEASES

Systemic diseases arising as a result of tonsillar infection are of 2 main varieties (1) those of a septic nature in which organisms, usually hemolytic streptococci gain access to the body through acutely inflamed tonsils and (2) those of a less clearly understood nature in which bacteria cannot be demonstrated in the more remote organs and tissues but which appear to be in some way related to infection of the tonsils themselves The former group the acute septic conditions are comparatively rare but examples of suppurative pericarditis pleurisy peritonitis arthritis and septicemia are occasionally seen Such events occur most frequently in the course of severe epidemics The latter group comprises a number of serious diseases among which may be mentioned rheumatic fever, rheumatoid arthritis glomerular nephritis various forms of non articular rheumatism infectious jaundice certain of the erythemas some cases of asthma and a variety of other conditions The mechanism involved in the pathogenesis of this group of diseases remains imperfectly understood Theories based on allergy or hypersensitiveness have many proponents Other investigators feel that, although certain of the manifestations of these diseases may be allergic in nature such an explanation is inadequate to account for the disease pictures in their entirety At the present time it is necessary to reserve judgment concerning the precise etiology of this entire group of diseases From the practical point of view the question of tonsillar infection in relation to systemic disease more or less resolves itself into a consideration of the indications for tonsillectomy

Indications for Tonsillectomy—While no hard and fast rules can be laid down which will serve as a guide in each individual case certain general principles can be stated The indications for tonsillectomy may be divided into two categories (1) local conditions in the throat (2) systemic diseases

(1) *Local Conditions*—Recurring attacks of acute tonsillitis peritonsillar abscess hypertrophy of the tonsils sufficient in degree to cause obstruction to breathing or to produce aural complications chronic cervical adenitis when other causes have been excluded

(2) *Systemic Diseases*—Tonsillectomy should be carefully considered in rheumatic fever glomerulonephritis early cases of rheumatoid arthritis and in the following conditions especially if there has been a history of preceding attacks of sore throat various forms of nonarticular rheumatism recurring attacks of bronchitis certain erythemas and symptomatic purpuras certain cases of bacterial asthma iritis which has proved refractory to other forms of treat

ment and a variety of other conditions In addition the procedure is sometimes indicated in patients who are underweight and in general poor health for no apparent reason In spite of this wide range of indications a conservative attitude should be adopted For example there is little evidence that tonsillectomy favorably affects the course of rheumatic fever and the procedure should be recommended more as a general health measure It should never be carried out during the active stages of this disease In rheumatoid arthritis tonsillectomy appears to be of some value in the early stages of the disease but in more chronic cases the results are usually disappointing In general it is the author s opinion that the question of focal infection has been greatly overemphasized in contemporary American medicine and that the time has come when the entire problem should be very critically reviewed

M H Dawson

ERYSIPELAS

Definition —Erysipelas is an acute inflammatory disease of the skin or more rarely, of the mucous membranes caused by the *Streptococcus haemolyticus* The dermal manifestation is accompanied by fever and constitutional symptoms

History.—The disease has been recognized since ancient times and its contagious nature has been known since the middle of the nineteenth century Fehleisen in 1882 demonstrated the streptococcus in the skin and reproduced the disease in animals and man by the inoculation of pure cultures In the preaseptic era erysipelas was a common and virulent infection frequently assuming epidemic proportions The introduction of a epsis did much to rid the disease of its terrors and in modern times epidemics have only occurred as the result of unhygienic conditions or the neglect of preventive measures

Another milestone in the history of erysipelas occurred with the introduction of modern chemotherapy the disease responds in dramatic fashion to the sulfonamide compounds and is now rarely a serious problem

Incidence —At present the disease is endemic in most communities its distribution corresponding with that of other hemolytic streptococcal infections It is more frequently encountered in temperate climates and in the spring of the year Individuals of all ages are susceptible the greatest incidence occurring between the ages of thirty five and fifty five years

Etiology —The exciting organism is *Streptococcus haemolyticus* The evidence strongly suggests that only organisms belonging to Group A (Lancefield) are implicated but strains belonging to any one of the twenty six or more types (Griffith) of Group A may act as initiating agents The concept of a specific erysipelas strain has been abandoned In occasional instances staphylococcus may give rise to a similar clinical picture

Infection always takes place at the site of a wound fissure or abrasion which is often too small to be visible to the naked eye It may be due to the introduction of organisms from external sources or to self infection as in chronic rhinitis and operations on infected areas A predisposing cause is lowering of resistance for any reason Patients who have recently undergone a surgical operation and women after parturition are particularly susceptible as well as patients with chronic alcoholism or debilitating disease

Morbid Anatomy —Microscopically the condition is one of edematous dermatitis with little fibrinous exudate and only moderate infiltration with leukocytes Suppuration takes place if the disease extends to the subcutaneous tissues Organisms are found only toward the margin of the lesion where they may occur in great numbers in the lymphatic spaces General sepsis is now rarely encountered

Symptoms —After a short incubation period of one to three days the disease sets in abruptly often with a chill accompanied by fever vomiting and symptoms of general toxemia—malaise headache and anorexia The dermal manifestation is usually noted simultaneously with or shortly before the appearance of general symptoms In 90 per cent of cases the local lesion is situated on the face usually beginning at the nostril or bridge of the nose occasionally on the lip or ear Other points of origin are the lower extremities usually from an abrasion or sore surgical wounds the umbilicus in the newborn and the vulva during the puerperium

Wherever it may start the local appearances are much the same A small area of

the skin becomes red and swollen and is tender on pressure The process spreads rapidly, the margins being sharply marked, elevated and indurated on *palpation*, constituting the characteristic "wall" In areas where the skin is very loose no 'wall' is formed Small vesicles or larger blebs frequently develop Small, red tonque shaped projections may be seen at the periphery, marking the advance of the disease in the *lymphatics Extension is always by* continuity, when this is apparently not the case careful inspection shows that the two inflamed areas are joined by reddened lymphatics Rarely two or more widely separated rashes are seen the result of multiple inoculation Involution takes place after a *few days in the parts first involved while* the process is still spreading at the periphery, the skin becomes paler and less swollen the blebs dry up into crusts, and finally there is a profuse flaky desquamation The regional lymph nodes are enlarged, but are difficult to palpate on account of the swelling of the overlying skin

In *facial erysipelas* the lesion spreads rapidly on the cheek and over the bridge of the nose to the opposite side giving the familiar 'butterfly' appearance The features are greatly distorted, the eyelids so swollen that the eyes cannot be opened the conjunctivae intensely reddened the skin of the face and ears swollen red tense and shiny and covered with vesicles or blebs On the forehead the process usually stops at the hair line in about 12 per cent of facial cases however it involves the scalp and does not stop until the nape of the neck is reached These natural stopping places of erysipelas are at the barriers where the skin is tightly bound down to the underlying structures For this reason erysipelas rarely passes down over the chin on to the front of the neck Occasionally it does not stop at the nape of the neck but extends to the back *it is then likely to spread over* wide areas and even over the entire body

In untreated cases the disease usually lasts from four to eight days Recrudescences and relapses are not uncommon and are ushered in by an increase or return of the fever In such cases there may be a recur*rence of* the inflammation at the site of last involvement rarely the parts first affected may be involved a second time Termination by crisis is common in untreated cases

The blood shows an increase in polymorphonuclear leukocytes Blood cultures are negative unless there is a complicating septicemia Erysipelas is a disease with a marked tendency to recur, as many as 20 per cent of patients have two or more attacks Occasionally, repeated attacks may occur and *in such* instances the skin may become greatly thickened as in elephantiasis and may remain in this condition permanently

Erysipelas of the mucous membranes is much less common It occurs chiefly in the pharynx and fauces, sometimes in the nose and is characterized by an intense diffuse redness and swelling with much pain Very rarely it occurs in the larynx and may lead to stenosis and death by suffocation The lesion may spread to the skin of the face but extension in the opposite direction *ie* from the skin to the mucous membranes is rare Occasionally the vulva is the primary site of erysipelas during the puerperium and extension often takes place to the adjacent skin more rarely to the endometrium

Complications —Abscess formation is by far the most common and important of the complications occurring in 10 per cent of untreated cases Sometimes the inflammation *leads to superficial gangrene or slough*ing especially over the ears the tip of the nose the ends of the fingers and toes Suppuration may take place in the frontal sinus or antrum further extension may occur and lead to thrombosis of the cavernous sinus meningitis or cerebral abscess Further com*plications may be expressions of a* septicemic process which is prone to occur in debilitated subjects

Preexisting chronic disease is sometimes favorably influenced by erysipelas *Occa*sionally malignant tumors undergo a pronounced recession or lupus of the skin or varicose ulcers may heal after an attack in leukemia the white count may drop temporarily to normal

Diagnosis —The characteristic appear*ance of the local eruption* especially of the sharply defined raised advancing margin the presence of vesicles on the surface and the inflammation of the neighboring lymph glands are usually quite *distinctive The*

combination of this lesion with the sudden onset of constitutional symptoms and high fever produce an unmistakable picture Occasionally a diffuse cellulitis or inflammatory edema extending from a carbuncle or furuncle may present a somewhat similar local appearance but the characteristic wall like margin is absent and constitutional symptoms are minimal Acute eczema and dermatitis may lead to confusion but in these conditions the skin is more indurated and less tender and constitutional symptoms are lacking

Prognosis —Erysipelas in the sporadic form as seen at the present time is an almost benign disease This is especially true since the introduction of the sulfonamide drugs Even in untreated cases the ordinary attack of erysipelas usually leads to complete recovery leaving no residue or defect. Formerly the mortality varied from 5 to 10 per cent, the great majority of fatal cases occurring in elderly debilitated or cachectic patients and in newborn infants

Prophylaxis —The patient should be isolated during the attack and the ordinary precautions of disinfection should be taken Cases of erysipelas should never be treated in the vicinity of surgical or maternity cases or by those in attendance on such cases

Treatment —The introduction of the sulfonamide compounds has rendered all other forms of treatment obsolete Sulfanilamide sulfathiazole and sulfadiazine are all effective but sulfadiazine produces fewer toxic reactions When these drugs are administered a prompt drop in temperature results the spread of inflammation is checked and complications seldom occur A dose of 6 Gm (90 grains) during the first twenty four hours followed by 3 to 4 Gm *daily for three to four days* is usually sufficient to check the disease The administration of an equal amount of sodium bicarbonate will prevent the development of renal toxicity due to the drug After the institution of treatment the temperature returns to normal within twenty four hours in approximately half of the cases and in only rare instances does fever persist for seventy two hours

Local applications are not needed apart from a simple greasing of the skin The use of serum therapy antitoxins and vaccines together with radiotherapy and ultraviolet light have been completely abandoned

The patient should be kept in bed on a bland diet until the temperature has been normal for two to three days Symptomatic medication may be needed, aspirin for headache and barbiturates for insomnia are usually sufficient

The tendency to *recurrent attacks* is best met by treatment of the chronic infection which is usually the cause (sinusitis eczema ringworm of the feet) The use of vaccines and streptococcal filtrates is recommended by some as a prophylactic measure

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(See also references under Streptococcal Infections Introduction)

SCARLET FEVER

Definition —Scarlet fever is an acute infectious disease caused by the *Streptococcus scarlatinae* and characterized by a sore throat and a punctate rash on the skin and roof of the mouth followed by desquamation

History.—Scarlet fever in early times was confounded with measles and rubella It was first definitely described by Sydenham in 1675 under the name of "febris scarlatinae" as a mild, harmless disease It was undoubtedly observed by Ballonius in a Paris epidemic of 1574 and in 1619 Sennert in Germany accurately described the disease The severe epidemics of diphtheria in the eighteenth century led to much confusion with scarlet fever and this in a measure was not cleared up until the discovery of the diphtheria bacillus

Incidence —*Age* —Scarlet fever is essentially a disease of early childhood The susceptibility is particularly great from the time of appearance of a positive Dick test to the eighth year According to McCollum the mortality is 33 per cent in the first year

about 25 per cent in the second and third years, and then gradually drops to 3 to 5 per cent in the eighth year where it remains throughout life The disease is practically unknown in the tropics

Race—The black race is relatively immune to the disease as compared with the white The yellow races also show an increased immunity as demonstrated by the Dick test

Seasonal Incidence—Epidemics are more common in the fall and winter, and gradually subside in the summer The relation between school attendance and the numerical distribution of scarlet fever cases during the year is very evident

Immunity—The newborn infant usually gives a negative reaction to the Dick test even when its mother gives a positive reaction for the infant has never become sensitized to the scarlatinal streptococcus This reaction to the Dick test corresponds to the negative tuberculin reaction of the nontuberculous infant The susceptibility in families seems to vary essentially with age Sometimes in large families when no quarantine is possible only a single member contracts the disease There is a definite tendency however for some families to react violently to scarlet fever three or more children dying in a relatively mild epidemic Certain families seem to be predisposed to the complicating nephritis Infants with exudative diathesis are particularly subject to a severe form of scarlet fever especially the anginose type

Other Diseases as Predisposing Factors—*Infections of the throat* seem to predispose to scarlet fever Schick cites three instances of scarlet fever *infection after* an attack of diphtheria in physicians who had previously worked in scarlet fever wards without contracting the disease Further predisposition to the disease seems to be caused by *surgical wounds puerperium* and *injuries* particularly burns

The Portal of Entry—That the pharynx is usually the portal of entry is evidenced by the primary localization there In exceptional cases the streptococcus of scarlet fever may enter through an operative wound a burn, the uterus at childbirth or an injury received during the postmortem examination of a scarlet fever patient

Etiology—The studies of Dick and Dick and of Dochez definitely established the etiologic relationship of the *Streptococcus haemolyticus* to the disease The evidence for this may be stated briefly *Streptococcus haemolyticus* is regularly found in the initial local lesion of the disease scarlet fever has been transmitted experimentally to man by inoculation with a pure culture of scarlatinal streptococci, the sterile filtrate from a broth culture of *S scarlatinae* causes a local reaction in the skin of persons susceptible to scarlet fever, but no reaction in those who are immune Toyoda and Fugati have shown that Dick s toxin contains both a heat labile and a heat stable toxin The latter toxin produces in certain individuals an allergic reaction that is probably responsible for the positive Dick tests in immune individuals If given subcutaneously to a susceptible person the sterile filtrate causes a general reaction with a typical scarlatinal exanthem immunization with the filtrate induces an active immunity to scarlet fever serum from *horses immunized with scarlatinal streptococci* specifically blanches the rash in scarlet fever neutralizes the toxin in the blood of patients and cures the toxic phase of the disease, convalescent scarlet fever serum *neutralizes the toxic action of culture filtrates*

Mode of Infection—In most cases infection occurs by direct contact The scarlet fever streptococcus can persist for weeks in garments, books toys and other articles and is thus more easily transmitted by a third party than are some of the other infectious diseases It can be conveyed by milk from cows infected with mastitis caused by *Streptococcus scarlatinae* or infected during its handling by an individual harboring the specific streptococcus Recent observations have shown that infection of the throat and pyogenic infections with *S scarlatinae* the so called *scarlatina sine exanthemata* are more frequent than had hitherto been supposed and that they may be an important factor in the spread of scarlet fever

The *incubation period* is variously estimated to last from one to eleven days it is occasionally longer the usual length of time being from two to five days

It is probable that scarlet fever is not communicable during the period of incuba

tion and that it is only slightly so at the onset of the disease The presence of discharges from the nose and throat should determine the length of quarantine In mild cases when discharges from the upper respiratory tract are absent an interval of three to four weeks seems to be sufficient to prevent the spread of the infection

Morbid Anatomy —The morbid anatomy of scarlet fever is not characteristic The typical renal lesions are characterized particularly by infiltration of the cortex with plasma cells around the glomeruli and the blood vessels Diffuse glomerular nephritis is characteristically associated with scarlet fever during the second and third weeks of the disease

Symptoms —The onset of scarlet fever is usually very abrupt Vomiting is one of the most constant early symptoms When seen soon after onset the patient has a high fever the skin is dry and there is a tendency for the cheeks to be reddened while a peculiar pallor is noticeable around the mouth and nose (circumoral pallor) The temperature generally rises very rapidly to between 103° and 105° F Although the face is flushed there is no definite *rash* until six to twenty four hours later when numerous fine red macules appear around the hair follicles and by confluence produce a deep blush of the skin The rash usually appears first on the neck behind the ears and on the chest gradually spreading within twenty four hours to the arms and legs In more severe cases it assumes a more definitely papular form resembling goose flesh because of the *localization around the hair follicles* When the scarlet fever is still more severe little vesicles may form on the papules In the mild cases and sometimes in a severe case it may be patchy and restricted to the soft folds of the axilla the elbow the groin and inner aspect of the thigh On the lower extremities small areas of a punctate rash around the hair follicles on the dorsum of the foot are often the only local evidence of a rash In *malignant scarlet fever* the rash often becomes hemorrhagic It can be entirely obliterated by pressure in the early stage the anemic area persists for a certain length of time the rash returning in pin points around the hair follicles on a definitely yellowish background (icteric) The skin usually feels hot and dry, and is slightly edematous Itching is a variable symptom not dependent on the severity of the rash Since in mild cases the rash may appear in small areas and persist for only a few hours it is of the utmost importance to examine the entire body repeatedly for its presence

Quite as characteristic as the rash is the *enanthem* on the soft palate and roof of the mouth which consists of a fine punctate eruption and is perhaps, the most constant sign of scarlet fever In the early stage the tongue is heavily furred tending to be red at the tip and sides the papillae are definitely enlarged and occasionally show through the thick fur in the center In the course of a few days the heavy white membrane desquamates leaving the tongue smooth and red with numerous large papillae on its surface—the so-called *raspberry* or *strawberry tongue*

The *pharyngeal symptoms* are definite although there may be only slight redness or injection of the fauces particularly in patients without tonsils If the tonsils are present there is generally definite swelling and in most instances a follicular exudate When the disease is severe the patches of membrane may coalesce so as to resemble that of diphtheria If in the first two days of the disease the membrane spreads beyond the tonsils it is often due to complicating diphtheria The swelling involves all of the pharyngeal structures

Secondary to the throat infection there is *swelling of the glands of the neck* particularly the so called tonsillar gland at the *angle of the jaw There is a general adenopathy* and in most cases the axillary inguinal and cubital glands are palpable

The *temperature* usually reaches its maximum within twenty four hours continues high for from three to five days and then gradually falls by lysis The height of the fever indicates the severity of the infection

The *pulse rate* usually ranges from 120 to 160 In the septic cases with marked cyanosis the pulse is very weak and can be felt only with difficulty

There is generally a very definite *polymorphonuclear leukocytosis* the white cell count varying from 15 000 to 30 000 or more The polymorphonuclear cells constitute from 85 to 95 per cent of the leukocytes Of particu

lar value is the relative increase of eosinophils to 5 per cent and above after an initial drop Mild cases of scarlet fever can often be distinguished from tonsillitis by the persisting eosinophilia A low leukocyte count and low eosinophils denote a bad prognosis

At the onset of the disease there is usually *mild albuminuria* with no further evidence of renal irritation The *involvement of the nervous system* is generally in proportion to the height of the fever *Diarrhea* occurring late in the septic type may be caused by streptococcic enteritis

Desquamation is one of the most typical signs of scarlet fever As a rule the degree is directly proportional to the severity of the rash The process begins on the chest and progresses as did the rash It is usually complete in from two to three weeks on the body and may continue for from four to seven weeks on the palms of the hands and soles of the feet When the disease is mild desquamation is later than when it is severe but usually there is an interval of from three to ten days between the disappearance of the rash and the first indication of desquamation During this period diagnosis of scarlet fever is sometimes very difficult and the only indication of the disease may be the breaks in the skin below the nails of the fingers and toes which can be seen when the ball of the finger or toe is pulled away from the nail In infants desquamation is usually insignificant Complete casts of hands and feet have formed in severe cases The secondary desquamation due to rapid drying of newly formed skin makes it difficult to determine the end of primary desquamation

Varieties of Scarlet Fever—Scarlet fever may be present without eruption fever angina or desquamation Mild scarlet fever is usually very difficult to recognize unless there is an epidemic There is generally a mild sore throat and a rash which develops only in patches in the folds and persists for from twelve to twenty four hours In mild epidemics a sore throat is often the only manifestation of the disease Sometimes there may be subsequent desquamation even if careful observation has revealed no rash Isolation of the specific streptococcus of scarlet fever helps to differentiate these cases An individual who gives a negative reaction to the Dick test may have tonsillitis caused by the *Streptococcus scarlatinae* This probably accounts for the frequency with which children come down with scarlet fever following tonsillitis in one of the parents

The *usual form* of scarlet fever is characterized by a sudden onset, with vomiting and a rise of temperature to 103° F within a few hours, followed by the appearance of a rash on the neck and chest which covers the entire trunk and extremities during the next two days, and persists for from four to five days before its gradual subsidence The desquamation as a rule begins eight or ten days after onset The throat usually shows the typical follicular tonsillitis, with considerable swelling of the fauces, and the typical punctate rash appears on the soft palate and roof of the mouth The characteristic strawberry tongue and moderate adenopathy are present The patient is usually very uncomfortable because of the high fever general malaise and painful sore throat Five or six days later, when the fever and sore throat have disappeared the patient feels ready to get up a fact which makes the subsequent isolation of about four weeks irksome and frequently very difficult to manage

Severe scarlet fever can be divided into the *fulminating toxic type* and the *anginose* or *septic type* In the first the patient is overwhelmed by the infection and dies within twenty four to forty eight hours from rapid heart failure without manifesting any very definite signs indicative of the disease The rash may be merely a blush with a patchy appearance over the trunk and extremities and none of the characteristic punctate features There is usually marked cyanosis and the patient is stuporous generally in a state of constant increasing delirium Another toxic type is manifested by high fever great restlessness headache delirium and an intense scarlet rash which is often hemorrhagic There may be hyperpyrexia the temperature rising to 108° or 110° F Death as a rule takes place within from forty eight to seventy two hours The two toxic types are due to the specific scarlet fever toxin and if treated early respond to the antitoxin

In the *anginose* or *septic form* of scarlet

fever the severity of the throat infection is the most striking feature The exudate from the tonsil becomes confluent and spreads to the other structures of the throat There is dysphagia and difficulty of respiration discharge of a profuse serosanguineous material from the nose and often early involvement of the paranasal sinuses and middle ear This condition resembles that of malignant diphtheria and the process may involve the larynx and trachea If death does not occur in this acutely septic state there may be marked sloughing of the throat with formation of deep abscesses and general sepsis Often a cuirass like swelling develops This type is seen more often in infants and young children

Sequelae —The sequelae of scarlet fever are so common that they have come to be regarded as merely a second phase of the disease (Pospischill s *Scharlach zweite Erkrankung*) which usually develops after an interval of from ten to fourteen days It is in this second period that the so called sequelae —otitis media sinusitis adenitis nephritis arthritis and gangrene—occur At the end of the first week the patient with the usual type of scarlet fever has a normal temperature and is free from symptoms but not until the fifth week has passed is he safe from the second phase

Angina Tonsillitis Cervical Adenitis and Cellulitis —As in the primary infection there may be very definite angina and tonsillitis associated with severe pain dysphagia and difficulty in speaking Peritonsillar and retro pharyngeal abscesses are not uncommon The infection particularly in young children may spread beyond the glands so that the entire neck is indurated The skin becomes tense and drawn the head is retracted and there may be considerable dyspnea caused by pressure on the trachea If death does not take place during the acute stage it is likely to result later from hemorrhage caused by ulceration into an artery or from pyemia produced by loosening of septic thrombi from one of the larger vessels of the neck

Otitis media one of the most common complications results from extension of the streptococcic infection in the throat to the middle ear and is characterized by rapidity of development The tendency of the streptococcus to destroy the drum membrane is responsible for the deafness which often results from scarlet fever Even when the drug is incised early the process may extend to the mastoid cells the lateral sinus the meninges or the brain

Nephritis —During the height of the acute febrile period there is only slight albuminuria without other evidence of renal irritation At times very severe throat complications are associated with a focal nephritis characterized by minute abscesses Typical nephritis develops during the second or third week of the disease but in exceptional instances may not appear until later It is found in about 10 per cent of all patients and in about 50 per cent of those with membranous angina Quite constantly preceding or accompanying the nephritis is the recurrent adenitis

Postscarlatinal nephritis is of three types—the mild the usual and the acute In a large percentage of the *mild cases* with sequelae affecting the throat and cervical glands the urine will show albumin and a few casts and at times even a few erythrocytes can be found There are no clinical signs of renal insufficiency except transient edema In the *usual cases* the symptoms are puffiness of the eyes edema of the lower limbs anorexia and pallor The urine may either contain only albumin and casts for a few days and then become hemorrhagic or may become suddenly dark reddish brown less abundant and loaded with albumin red blood cells and casts This condition may continue for a number of weeks before the nephritis gradually disappears or exceptionally may become chronic At any time during the acute course the kidneys may cease to function and signs of uremia appear In *acute cases* the course is extremely rapid The first indication of renal insufficiency may be a convulsion There is constant nausea and vomiting fever restlessness and convulsions The urinary secretion may cease entirely or the urine may be scanty bloody filled with casts and red blood cells and coagulate solidly on heating With proper treatment it is surprising how many children recover from this acute uremia Certain families seem especially vulnerable to nephritis but in spite of the fact that it is severe and often long continued there is a very good outlook for complete recovery.

McCollum found that nephritis became chronic in only 20 of 5000 cases

Arthritis —There are two types of scarlatinal arthritis the first a severe but fortunately rare complication is septic and suppurative being a manifestation of the generalized streptococcal septicemia which usually involves the larger joints and is often multiple the second and ordinary form the so called scarlatinal synovitis is very common in some epidemics usually appearing at the end of ten days in the wrists hands elbows, and knees It is manifested by redness some pain, and swelling due to synovial distention As a rule there is spontaneous recovery in the course of a week

Cardiac Complications —The cardiac complications which are most common in the severe toxic and septic cases result from marked fatty degeneration of the myocardium Sudden disappearance of the more or less intense rash usually indicates heart failure In the septic form malignant endocarditis may be associated with purulent pericarditis More frequently simple endocarditis develops which corresponds more closely to the rheumatic endocarditis

Complications of the Respiratory Tract — Purulent sinusitis is a frequent complication of septic fever Considering the severity of the throat infection it is surprising how seldom bronchopneumonia complicates scarlet fever The streptococcus of scarlet fever apparently has no tendency to localize in the lung Empyema is occasionally a complication

Involvement of the Central Nervous System —Osler, in discussing a series of 120 cases of infantile hemiplegia reports that 7 developed during scarlet fever *Meningitis* results either by direct extension from the ear or the accessory sinuses, or is caused by septic emboli endocarditis, or thrombosis In the more toxic conditions *acute mania* may develop As a postscarlatinal condition *encephalitis* is rare

Numerous cases of *gangrene* have been reported which involve small areas of the skin the hands or feet and occasionally an entire extremity The process is often fatal

Paronychia occurs frequently during desquamation Children and adults too constantly pull off the dead epithelium and many fissures are caused by rapid drying of the new skin Infection through these may give rise to a generalized *impetigo contagiosa*

Relapses, Recurrences, and Second Attacks —As a rule, one attack of scarlet fever gives immunity for life The fact that so many individuals who are exposed to the disease do not contract it suggests that much scarlet fever is unrecognized A patient having more than two attacks of so called 'scarlet fever' is very likely to be suffering from some other disease McCollum reports 15 relapses in 5000 cases thirty to thirty five days after the disappearance of the eruption Lichtenstein states that relapses are due to exogenous cross infection in patients who become immunized very slowly as indicated by a persisting positive Dick test after an attack

Relationship to Other Diseases —The relationship of diphtheria to scarlet fever in patients suffering with the latter is unsolved A recent study has demonstrated that immunity to diphtheria as shown by a negative Schick test may be lost during the course of scarlet fever In eight of 219 cases of scarlet fever in which the Schick test was negative it became positive during the course of the disease The mortality of the diphtheria complicating scarlet fever is about twice as high as that of the usual type

Diagnosis —The diagnosis must usually be made clinically Abrupt onset usually with vomiting rapidly rising temperature sore throat evidenced often by a follicular tonsillitis and marked reddening of the entire fauces the punctate rash on the hard palate followed in from twelve to twenty four hours by a finely punctate blush on the neck and chest which spreads gradually over the entire body, with the characteristic strawberry tongue and subsequent desquamation are so characteristic that it is easy to recognize the normal cases The difficulties are presented by the very mild and very severe forms In mild cases the insignificance of the general symptoms the inconsequential nature of the rash and the fact that it is patchy and seemingly due to local irritation rather than to systemic disturbance makes recognition very difficult A sore throat with a definite punctate rash on the roof of the mouth and soft palate associated with the scarlatiniform rash must

be considered evidence of scarlet fever The localization of the rash in the groins axillae and folds of the elbow may be of diagnostic aid in the mild cases Just as difficult of interpretation are the overwhelming toxemias without rash The rash on the roof of the mouth is usually present although it, too may be absent Careful search of the entire body surface may reveal small patches of erythema Equally difficult to recognize particularly in younger children is the septic streptococcal tonsillitis in which no rash is found even on repeated daily examination but which produces desquamation by the end of the second week

Of some value in differential diagnosis is the *Leede Rumpel phenomenon* which consists of spontaneous hemorrhage in the fold of the elbow after constriction of the upper arm with a rubber band This always occurs in scarlet fever The *Schultz Charlton phenomenon* is of pathognomonic significance it consists in the complete disappearance of the rash in from four to six hours in an area about the size of a dollar when the serum of an individual who has recovered from scarlet fever is injected intracutaneously Dick has shown that this always takes place when the serum is taken from an individual immune to scarlet fever even when there has been no previous attack

Differential Diagnosis—DERMATITIS EXFOLIATIVA—The differentiation of scarlet fever from dermatitis exfoliativa (scarlatiniforme) is difficult for this disease simulates very accurately the anginose as well as the cutaneous manifestations of scarlet fever Its onset is sudden and accompanied by fever and sore throat Desquamation of the tongue occurs and an eruption which is indistinguishable from that of scarlet fever develops and is followed by similar desquamation A primary attack of this disease is practically always mistaken for scarlet fever Its recurrent nature is the distinguishing feature Third or fourth attacks of scarlet fever are usually dermatitis scarlatiniforme

Measles—It is rarely difficult to distinguish measles from scarlet fever The simultaneous presence of both in the same individual is sometimes difficult to recognize At the onset of measles there is occasionally a scarlet like rash on the chest which precedes by some hours the typical eruption on the face the so-called preeruptive rash of measles' which may be difficult to distinguish from that of scarlet fever

RUBELLA—Differentiation of mild scarlet fever and moderately severe rubella is often difficult The rash of rubella may resemble in every way the fine punctate rash of scarlet fever Its distribution is characteristic, however since in rubella it is usually on the face where it is absent in scarlet fever The angina is usually less severe but the swelling of the posterior cervical glands more marked

The rash of *erythema subitum* may resemble very closely that of scarlet fever The characteristic appearance of the rash just after the fall of temperature distinguishes it very definitely from that of scarlet fever Desquamation is usually slight.

TONSILLITIS.—The differentiation from severe follicular tonsillitis with marked systemic reaction particularly in young children is practically impossible The differences in toxin production of various strains of streptococci may account for variations in the intensity of the rash

SMALLPOX CHICKENPOX—In smallpox and chickenpox there may be a prodromal rash which resembles in no slight degree that of scarlet fever The rapid appearance of the typical vesicular lesions usually renders diagnosis clear

DIPHTHERIA—The difficulty in distinguishing diphtheria from scarlet fever depends largely upon the type of membrane in the throat Although the two diseases may coexist and develop at the same time as a rule diphtheria occurs late in the course of scarlet fever The character of the membrane and its extent may help identification but only the demonstration of the *Corynebacterium diphtheriae* bacillus can establish diagnosis A membranous angina occurring late in scarlet fever is usually diphtheritic

RASH DUE TO DRUGS—The rash produced by *quinine* in certain susceptible individuals may be punctate in character resembling scarlet fever not only in itself but in the ensuing desquamation The absence of any throat symptoms and the taking of the drug are the differential features *Atropine* similarly may cause an eruption very comparable to that of scarlet fever The dilated pupils dryness of the mouth peculiar patchy blush of the face and absence of any throat

symptoms other than the dryness usually differentiate the two conditions *Aspirin* may produce an erythematous rash with the circumoral pallor The *iodides iodoform luminal* and *copaiba* may also produce a confusing rash

Anaphylactic Rashes —Most typical of the anaphylactic rashes is the *serum erythema* which appears a week or ten days after the injection of serum The rash may be morbilliform but is often typically scarlatinal in appearance and distribution It usually spreads over the entire body very much more rapidly than does the rash typical of scarlet fever The *ingestion of certain foods* (shellfish strawberries etc) may give rise to a rash indistinguishable from that of scarlet fever Knowledge of this idiosyncrasy together with complete absence of throat symptoms, usually establishes the diagnosis

In infancy and childhood the *erythemas caused by febrile disease* especially throat infections by *strenuous crying* by *irritating compresses bandages* or *ointments* or by *heat* may produce a skin picture more or less closely resembling that of scarlet fever The absence of other symptoms and a local cause for the rash usually makes the differentiation easy

Prognosis —The prognosis in scarlet fever is very uncertain The older the patient the better the prognosis The general conditions of hygiene seem definitely to influence the mortality McCollum s figures show for Boston over a period of twenty years a mortality rate varying from 1 to 6 per cent Hospitalization of scarlet fever patients in large cities has markedly reduced the number of deaths

The prognosis in the toxic type is usually grave, but is much better if antitoxin is administered early Hyperpyrexia cyanosis coolness of the skin with patchy erythema marked early swelling of the lymph glands and the tendency to bleed from the throat and into the skin are of very serious import especially when they occur early in the disease The second period of danger is during the second phase of the disease The prognosis for children who develop nephritis even if they have had convulsions is relatively good with proper treatment

Prophylaxis —Immediate isolation of every scarlet fever patient either at home or in a contagious hospital, is essential If the patient remains at home, individuals not directly exposed may be allowed their liberty if they show no symptoms at the end of eleven days The danger of carrying scarlet fever is such that the physician should always wear a gown roll the sleeves to the elbow during physical examination and thoroughly scrub his hands after leaving the patient

When the patient has recovered everything that can be washed should be thoroughly cleaned with soap and water Books and playthings must be burned Bed clothing should be boiled or fumigated in a confined space

Specific Prophylaxis —Susceptible individuals those manifesting a positive Dick test may be actively immunized by the subcutaneous injection of scarlet fever streptococcus toxin Dick advises the use of five injections of 500 2000 8000, 25 000 and 100 000 skin test doses of toxin at five- to seven-day intervals Although this amount is undoubtedly necessary for permanent immunity temporary immunity can be achieved by much smaller doses as is shown in the report of Keefer It would appear preferable to give an initial series of three injections of 500 2000 and 10 000 to 20 000 skin test doses followed after two weeks by a retest and to continue further immunization only in those who are still Dick positive As a general public health measure active immunization in its present form cannot be advised Active immunization is especially valuable in checking local outbreaks of scarlet fever in schools small communities etc and for the protection of those intimately exposed to the disease for limited periods of time Passive immunization by the administration of 2000 units of scarlatinal streptococcus antitoxin may be indicated in special instances Because it may have to be repeated at the end of two weeks a mixed convalescent serum is preferable for this purpose It is given intramuscularly in doses of 10 to 20 cc The general use of the antitoxin for prophylactic purposes is not advisable because of the relatively short duration of the protection and the low communicability of scarlet fever Children or others exposed to scarlet fever should be watched closely for sore throat

or other symptoms of the disease and the temperature should be taken twice daily

Treatment.—If rigid quarantine cannot be enforced at home patients should be sent to an isolation hospital Since in the early stages scarlet fever is not very contagious immediate isolation protects other members of the household In the home adequate isolation is practically impossible unless both patient and nurse can be quarantined in a room with adjoining bath The nurse should have special instruction in the care of infectious diseases and in aseptic technic Carpets rugs and hangings should be

As soon as desquamation starts the patient should be anointed each day with liquid petrolatum and washed every second day with soap If there is much itching menthol may be added to the petrolatum At the end of three weeks if the temperature has remained normal and no complications have developed, the patient may be allowed to get up one hour each day This period may be increased one hour a day thereafter

The urine should be examined daily during the first month and carefully examined once a week for at least two months after the

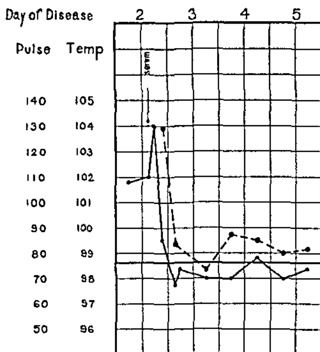


Fig 18—Scarlet fever treated with serum on second day of disease Immediate drop of temperature to normal Pulse curve is made of a series of dashes

removed and all unnecessary articles taken from the room Scarlet fever is a self limited disease so that in the mild cases general therapy alone is necessary The patient should be made as comfortable as possible and kept in bed for three weeks The bowels should be kept open and plenty of fluids consisting of fruit juices and water given in addition to the ordinary soft diet Pospischill who studied the effect of diet in a large series of carefully controlled cases was unable to determine that the incidence of nephritis was higher when a full diet was given than when milk only was allowed

illness because occasionally renal complications develop after an interval of several months At the end of four weeks if desquamation is complete and there are no discharges from nose mouth or ears the quarantine may be terminated The so called return cases are probably due to persisting infection in the nose and ears rather than to infection from scales

Specific Treatment—The first effective serum of this type was that produced by Moser in 1902 Scarlatinal antitoxin when given in adequate doses in the acute toxic phase of scarlet fever usually causes a

prompt abatement of the toxic symptoms and disappearance of the rash within twenty-four to thirty six hours There is frequently also a sharp drop in temperature and pulse rate and a diminution of the leukocyte count In addition, the antitoxin seems to lessen *the number of septic complications* and to diminish their severity when used during the acute toxic phase of the disease It appears, however to have no beneficial effect on postscarlatinal sepsis after the rash has faded The dose varies from 6000 to 80,000 units (1 unit is the amount of anti toxin necessary to neutralize 50 human skin test doses) depending upon the size of the patient and the severity of the disease The antitoxin is usually given intramuscularly but may be used intravenously in extremely toxic cases after desensitization which if properly carried out takes a considerable number of hours Severe anaphylactic reactions have been greatly reduced by the use of refined antitoxin Toomey calls at tention to the mild character of scarlet fever in the last decade and emphasizes the point that only after an epidemic with a high mor tality rate will it be possible to state defi nitely the value of the antitoxin Early ad ministration of the serum is essential for satisfactory results Recently there has been a revival in the use of convalescent serum in the treatment of the toxemia In many cities the development of serum centers which collect and distribute a pooled con valescent serum has made it widely avail able Given in the first forty eight hours in doses of 40 to 100 cc it produces results that often are as striking as are those which follow the administration of antitoxin It is best given intravenously but can be given intramuscularly It should be carefully warmed to body temperature and given over a period of about twenty minutes

The use of sulfonamides has been of great value in the reduction of the septic mani festations of the disease These drugs have no effect on the neutralization of the soluble toxin produced by the *Streptococcus scar latinae* but by inhibiting its growth they limit the toxin production and its local and general septic effects

Sulfanilamide or sulfadiazine should there fore be given at the earliest moment in ad dition to the serum in moderate and severe cases and alone in mild cases in which the initial temperature is less than 101.5° F The daily dosage recommended by Long and Bliss is ⅗ grain (0 04 Gm) per pound of body weight for the adult and 1 grain (0 065 Gm) per pound for the infant weigh ing less than 20 pounds (9 Kg) This dos age is given until the temperature has been normal for two or three days when it is gradually reduced to ⅖ grain (0 026 Gm) *per pound three times a day for the adult* and ⅕ to ³⁄₁₀ grain (0 013–0 018 Gm) per pound three times a day for the child Either sulfanilamide or sulfadiazine may be used preferably the latter because it has less tendency to produce toxic reaction

Symptomatic Treatment —For the almost constantly present cervical adenopathy the ice bag is used It is well to apply this early and not to wait until the glands are swollen The proper fitting of the ice bag particu larly in children, is essential Cold compresses, which can be used in the same way should be tied over the head rather than around the neck so as to reach the inflamed glands successfully They ought to be changed every two hours during the day and once during the night In the later stages par ticularly if cold is not well tolerated heat (a rolled up woolen cloth wrung out in hot water) applied in the same manner often relieves pain and causes rapid disappearance of the glandular swelling If the glands have begun to break down large hot compresses should be used and renewed every fifteen minutes for alternate hours Bullowa has suggested that tonsils so placed that the act of swallowing tends to milk their contents into the lymph channels should be removed even in the acute stage of scarlet fever This would seem to be indicated only in the exceptional case

It is desirable for older children and adults to gargle with a mild antiseptic solution every three or four hours For smaller chil dren or when gargling is painful irrigation of the throat with warm normal saline boric acid or dilute antiseptic solution (sev eral quarts) gives very apparent relief Such treatment is desirable in the moderate as well as in the most severe septic cases Ap plication of strong antiseptic solutions is contraindicated The nose should be kept clean and in case of crusting a few drops

of a 0 25 per cent preparation of menthol in liquid albolene inserted several times a day Cultures should be taken from the throat so as to exclude the possibility of diphtheritic infection and permit immedi ate administration of antitoxin if they are positive The ears must be examined daily even when there is no complaint As soon as there is an injection of the drum 7 per cent carbolated glycerin should be instilled into the ear filling the entire canal and a small ball of cotton saturated with the solu tion inserted in the canal as a plug As soon as there is bulging the drum should be widely incised If the discharge be sero sanguineous no irrigation is necessary, if purulent the ear should be washed with sterile salt solution or boric acid three times a day In young children tenderness and edema develop above the ear (subperiosteal abscess) instead of over the mastoid process The mastoiditis complicating scarlet fever should receive early operative treatment

For the toxic conditions with marked cyanosis caffeine in frequently repeated doses camphorated oil or digifolin given hy podermically is of some value

The mild nephritis usually needs no special treatment The patient should be kept in bed on a low protein salt free diet The indication for immediate treatment is the rapid development of uremia Removal of blood (250 cc in five year-old children 300 cc in ten year old children and 500 cc in adults) followed by an equal injec tion of salt solution usually brings the pa tient out of a state of coma and relieves the convulsions It may be necessary to repeat such treatment If the symptoms are due to edema of the brain the intravenous use of magnesium sulfate or hypertonic sugar solution will relieve the condition

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BACTEREMIA

(*Septicemia*)

Definition —Bacteremia or septicemia is a feature of various infections and the only reason for discussing the subject separately is to direct attention to its significance in diagnosis and prognosis When bacteria are isolated from the circulating blood bacteremia is present Septicemia is frequently used synonymously with bacteremia al though it implies to some that bacteria are actually multiplying in the circulating blood It seems unlikely that bacteria ever multi ply in the circulating blood except under unusual circumstances such as in pre agonal states or when the focus of infection is intra vascular In any event the presence of micro organisms in the circulating blood should always raise the question of their source or their portal of entry

In general it can be said that bacteremia indicates a temporary loss of equilibrium be tween the local defense mechanism at the site of infection and the general immune and blood clearing mechanism of the body Bac teremia is of greatest value in diagnosis when symptoms of infection are present without localizing signs as in typhoid fever or undulant fever It is of the highest importance in prognosis when there is a recognized focus of infection with an associated

invasion of the blood stream, since bacteremia under these conditions indicates that there has been a breakdown of the normal defense mechanisms of the body

Etiology —The organisms that most commonly invade the blood are the hemolytic streptococcus, the staphylococcus the pneumococcus and the colon bacillus Less frequently one encounters such organisms as the gonococcus, meningococcus the *Bacillus mucosus capsulatus* or the influenza bacillus

Portal of Entry —The common portals of entry for bacteremia are the middle ear and mastoid process the skin the throat, and the genito urinary tract Less often the biliary tract and the bones are portals of entry The gastro intestinal tract is rarely a source of bacteremia except in cases of typhoid fever All these regions should be investigated for the possible source of infection in any patient with bacteremia It should always be remembered that infection of the endocardium may cause bacteremia without any other portal of entry being obvious

Pathogenesis —Bacteria enter the circulating blood directly by way of the lymphatics or the capillaries leading away from the original focus of infection Once they enter the blood stream the normal clearing mechanism of the body attempts to remove them as rapidly as possible This is accomplished in large part by the reticulo endothelial cells of the body which are located in the liver spleen, lymph nodes bone marrow and to a lesser extent in other tissues Once organisms have lodged in the various tissues of the body one of these things may follow they may serve as secondary foci of infection for bacteremia they may be destroyed without causing destruction of tissue or they may set up foci of suppuration (metastases)

Micro organisms may enter the blood stream from a focus of infection when an infected thrombophlebitis develops in the region of the infection or when the local defense mechanism is insufficient to prevent the spread of organisms They frequently enter the blood stream when the local defense mechanism has been ruptured such as following surgical incision and drainage or when the tissue is injured *in the neighbor*hood of an infection

It is well to remember, then, that the presence of bacteria in the circulating blood suggests an inadequate local defense mechanism at the site of the infection a thrombophlebitis, or several foci of infection

Morbid Anatomy —The changes in the organs seen postmortem vary with the type of infecting organism, the duration of the illness and the number of foci of infection When death occurs very rapidly—that is within a few days of the onset of the illness —there may be very few signs to indicate the cause of death There may be small hemorrhages in the skin or in the serous membranes The spleen is often enlarged and soft The liver may show some enlargement with cloudy swelling and focal areas of necrosis The kidneys may be swollen and studded with hemorrhages or small abscesses In hemolytic streptococcus or *Bacillus welchii* infections there may be evidence of excessive hemolysis of blood with hemoglobin staining of the tissues and jaundice

When the patient lives long enough and metastases develop abscesses and infected infarcts may be found in various organs such as the lungs, the kidneys the muscles or other organs

Symptoms and Signs —There are no distinctive symptoms or signs of bacteremia since identical clinical features may be present in infections with and without bacteremia The possibility should be considered in any patient who has fever without localized signs of infection or chills fever and sweats associated with evidence of one or more foci of infection Finally bacteremia should be suspected in all patients with symptoms and signs of infection who develop skin eruptions, arthritis splenomegaly jaundice multiple areas of bronchopneumonia or abscesses in the muscles or bones during the course of the infection Clues may be obtained if there is a history of a recent infection of the skin (furuncle infected wound) sore throat or otitis media Infections of the uterus following an abortion and infections of the genito urinary tract should be looked for The possibility of osteomyelitis should always be considered

The following points in the *clinical history* or *physical examination* may suggest bacteremia but they do not establish the diagnosis In any patient suspected of hav

ing bacteremia one should ascertain whether there have been infections in the past which might serve as a portal of entry Of particular importance are infections of the skin such as boils carbuncles paronychia or infected wounds infections of the throat middle ear or mastoid process infection of the genito urinary tract such as pyelitis pelvic inflammatory disease or gonorrhea previous operations for infections such as extraction of teeth catheterization of the bladder or surgical incision and drainage of an abscess or any other infection and previous pulmonary infections

In the *physical examination* the following features suggest the presence of a bacteremia

1 Continuous or irregular fever with or without chills and sweats but without any local signs of infection In all such patients a blood culture should be made

2 Hemorrhages into the skin conjunctivae or mucous membranes

3 Acute monarticular or polyarticular arthritis or pain in the bones

4 Signs of pulmonary infarction or diffuse bronchopneumonia

5 Signs of endocarditis that is evidence of valvular heart disease splenomegaly or embolic phenomena

6 Signs of pelvic infection in women or prostatic or urinary tract infection in men

If any of the above symptoms and signs are associated with a progressive anemia jaundice and leukocytosis the possibility of a bacteremia is much more suggestive

When there is any question of a bacteremia being present a blood culture should be made at once

The *onset* of bacteremia may be abrupt with chills and fever irregular or continuous Some patients are perfectly clear mentally while others soon show delirium Headache often with vomiting and meningismus is common and in some forms of sepsis meningitis is an outstanding feature This is especially true of cases of pneumococcus bacteremia and of streptococcus bacteremia following otitis media and mastoiditis

Skin eruptions are frequent and important in diagnosis Petechial hemorrhages into the skin and conjunctivae are most often encountered Erythematous and even papular and vesicular eruptions are not infrequent Jaundice due to blood destruction and depressed liver function is an occasional outstanding feature and abscesses of the skin and subcutaneous tissues are not infrequent

Pains in the joints and true arthritis are common manifestations of streptococcus meningococcus and gonococcus bacteremia

The *bones* and *muscles* should be examined for evidence of infection such as osteomyelitis or abscesses of the muscles

The *lungs* may show multiple areas of bronchopneumonia or pulmonary infarcts and empyema Bronchopneumonia is common in hemolytic streptococcus and staphylococcus sepsis and pulmonary infarction is especially frequent in thrombophlebitic types of sepsis arising in the pelvic veins or cranial sinuses Infarcts are also frequent in thrombophlebitis of the tonsillar and renal veins

Pericarditis is occasionally encountered when there is an infection in the adjacent lung or heart

The *heart rate* is usually accelerated and when endocarditis is present a murmur is usually but not always present

The *abdomen* may be distended and anorexia and vomiting can be prominent features The spleen is generally enlarged but it is not always palpable during life

Blood Examination—In most patients with bacteremia there is a rapidly progressing anemia with leukocytosis A normal or depressed leukocyte count is by no means uncommon but there is generally an increase in the polymorphonuclear leukocytes An increase in the icteric index is found when hemolysis is progressing at a rapid rate

Urine—Albuminuria is present in most cases and hematuria and pyuria are less frequent Occasionally one can isolate the same organism from the urine as from the blood

Diagnosis—The diagnosis of bacteremia is established by culturing micro organisms from the circulating blood The blood should be withdrawn under sterile conditions and inoculated in flasks of broth as well as in melted agar for pour plates When the question of anaerobic bacterial infection arises the blood should be cultured under conditions suitable for growing anaerobic organisms

Prognosis—The outlook in patients with bacteremia is always grave and the fatality rate in patients with infections associated with bacteremia is always higher than in those without it Factors influencing prognosis when bacteremia is present depend upon the summation of such factors as the site of the primary focus of infection the age of the patient the species of microorganism, the presence of associated debilitating disease the accessibility of foci of infection for surgical drainage and the type of treatment All these factors must be taken into account in assessing the prognosis of any patient with bacteremia

Treatment—The treatment of patients with bacteremia must be directed along three lines general supportive and symptomatic treatment, the use of specific measures that aid in the clearing of the blood and focalizing the infection, and the removal or drainage of foci of infection

General and Symptomatic Treatment—All these patients should receive expert nursing care The food intake should be increased insofar as possible in order to maintain the nutrition status of the patient and fluids should be forced so that the twenty four hour urinary output is at least 1500 cc Blood transfusions of 500 cc each should be given to all patients who develop an anemia below 70 per cent hemoglobin (10 5 Gm per 100 cc) Sedatives should be given for headache and the skin should be kept clean and in good condition

Specific Measures that Aid in Clearing the Blood of Organisms and Focalizing the Infection—CHEMOTHERAPY—Since the introduction of the sulfonamides the fatality rate in patients with bacteremia has decreased, so that all such patients should receive some form of sulfonamide therapy The drug of choice at present in the treatment of bacteremia regardless of its cause is sulfadiazine largely because it is pleasanter for the patient to take and there are fewer side reactions such as anemia leukopenia drug fever and skin eruptions Renal complications are less frequent than when sulfapyridine or sulfathiazole is given but they will occur unless the fluid intake is forced so that the daily urinary output is at least 1000 to 1500 cc In a few patients renal injury follows the administration of sulfadiazine in spite of an adequate fluid intake When sulfadiazine is not available the drug of choice is sulfathiazole These drugs should be given so that the concentration in the blood is at least 10–12 mg per 100 cc for sulfadiazine and 8–10 mg per 100 cc for sulfathiazole

This can usually be accomplished by an initial dose of 4 Gm (60 gr), followed by doses of 1 Gm every four hours When this dosage fails to produce maximal concentration in the blood it must be increased

If patients are unable to take the drug by mouth, the sodium salt of sulfadiazine or sulfathiazole may be given intravenously, dissolved in sterile distilled water in a concentration of 5 Gm in 100 cc When the drug is given intravenously one must be certain that the fluid balance is such that the twenty four hour output of urine is at least 1000 cc

For children, the daily dosage should be arranged so that 0 2 Gm per kilogram of body weight or 1.5 grains per pound should be given during the twenty four hour period

Serum Therapy—Serum treatment is of value in pneumococcus and meningococcus bacteremia but it is needed less often now than before the introduction of the sulfonamides Some success has been reported following the use of anti staphylococcus serum (Julianelle) in cases of staphylococcus sepsis Other sera are of little value in the treatment of bacteremia

Removal or Drainage of Foci of Infection—The removal or drainage of foci of infection is important in any patient with focalized infection and bacteremia but one must be certain that the infection is well localized and that it can be drained without rupturing the local defense mechanism That is to say, incision should not be carried beyond the wall of any abscess These are problems that must be handled by a competent surgeon

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FOCAL INFECTIONS

The term 'focal infection was coined by Frank Billings who, in his classic contribution "Chronic Focal Infections and Their Etiologic Relations to Arthritis and Nephritis' was really the originator of the theory of focal infection Focal infection may be defined as a localized infection which presumably produces symptoms in other parts of the body and in which there is usually no demonstrable bacteria in the blood stream This distinction however cannot always be made For example one of the commonest of the focal infections is that produced by the gonococcus in the posterior urethra or in the prostate gland with secondary involvement of the joints in the form of gonococcal arthritis In such a condition the gonococcus has of course reached the joint by way of the blood stream but in the vast majority of cases this fleeting bacteriemia cannot be demonstrated by blood cultures

At the present time nearly thirty years after the publication of Billings article focal infection has come to occupy a very important place in the activities of medical and surgical practice and the various specialties Many thoughtful physicians however who originally accepted the theory of focal infection with enthusiasm have watched with interest and some trepidation its rapid development in the various fields of medicine and are now wondering if the time has not arrived for a revaluation of the theory Many students today question seriously its validity and some are quite willing to throw it completely overboard This is particularly true in Europe where the idea of focal infection has never met with enthusiastic acceptance But even in America many practitioners are becoming a little wearied of the theory which has been accepted as if it were an established fact

Etiology.—The original theory of focal infection as propounded by Billings was to the effect that foci of infection in the tonsils teeth sinuses and other sites may produce disturbances in distant parts of the body such as the joints or kidneys by means of a toxin which presumably circulates through the blood stream Such a toxin, however has never been demonstrated

Foci of infection have been assumed to play a role in many diseases such as arthritis iritis rheumatic fever nephritis heart disease and bronchiectasis It is probably in connection with rheumatoid arthritis however that the theory has been most intimately associated In 1938 the writer in collaboration with D M Angevine analyzed 200 cases of rheumatoid arthritis and found that definite foci of infection existed in only 20 per cent of them It is quite obvious that the incidence of focal infections in patients with arthritis and other systemic diseases varies widely depending on the type of patient studied For example foci of infection would be quite prevalent in patients selected from a large city hospital while the same number of patients from private practice would reveal comparatively few

By far the commonest micro-organism involved in focal infection is the streptococcus either the *Streptococcus haemolyticus* or the *Streptococcus viridans* the gonococcus staphylococcus and pneumococcus come next in order The colon bacillus is not an infrequent cause of focal infections in the abdominal cavity or in the genito urinary tract It is axiomatic of course that all infections have an original portal of entry through which micro-organisms gain access to the body The portal of entry may be the site of a very fleeting infection such as an acute coryza or influenza or it may be that of a chronic focus such as a chronic sinusitis or apical abscess of a tooth

Morbid Anatomy—A focus of infection may be localized in any part of the body but most commonly it occurs in the tonsils or about the teeth Foci in the tonsils are much more prevalent in children and adolescents while root abscesses about the teeth are usually but not always discovered in elderly persons Other important locations for focal infection are the accessory nasal sinuses the genito urinary tract, the

gallbladder and occasionally the appendix In the intestine itself, ulcerative colitis and diverticulitis may produce symptoms in the joints and other parts of the body Bronchiectasis occasionally acts as a focus of infection

Symptoms—Many conditions have been suspected of being caused by foci of infection The most common are subacute and chronic arthritis of the infectious type and rheumatoid arthritis however, the kindred rheumatic conditions, such as myositis, fibrositis and neuritis have also been included Acute glomerular nephritis and inflammatory lesions of the eye such as iritis, uveitis keratitis and choroiditis have been attributed to focal infection Other less common diseases which may be related to foci of infection are erythema nodosum phlebitis, perinephritic abscess and possibly pyelitis Conditions which are much more plausibly attributed to focal infection are general debility loss of weight secondary anemia fatigue and muscular weakness Furthermore a focal infection may lower the resistance to a disease of which it is not the cause, and removal of foci may therefore be an important measure in the treatment of chronic systemic diseases such as tuberculosis syphilis and diabetes

Diagnosis—The diagnosis can often be made by simple inspection For example, highly infected tonsils present an unmistakable picture However there have been a great many instances of presumptive diagnoses in respect to focal infection It is very difficult at times to decide whether tonsils are actually infected, or whether they have undergone a simple hyperplasia A frankly suppurative sinusitis is easily recognized but low grade infections of the sinus are often identified with considerable difficulty The same is true of root abscesses about devitalized teeth In many cases the decision of whether a root abscess actually exists is difficult to arrive at even after the most careful x ray study The demonstration of pus or pus cells and the cultivation of pathogenic bacteria from a suspected focus will always do much to confirm the diagnosis of a genuine focus of infection

Prognosis—Removal of a focus of infection may be followed by relief of remote symptoms Unfortunately this is not always the rule The improvement may be rapid or gradual and is sometimes preceded by an exacerbation of the symptoms immediately following the removal of the focus Prediction of improvement should be made with care and promise of cure should not be held out in diseases of which the cause is still unknown

Treatment—An obvious focus of infection should usually be removed provided the health of the patient permits such removal without too much risk of disaster If the tonsils are acutely inflamed it is better to wait several weeks until the activity of the infection has subsided before removing them The same applies to all operative procedures in the presence of the various acute infectious diseases especially rheumatic fever If many teeth are infected only one or two should be extracted at a time Very anemic patients should receive a transfusion of blood before operation In rheumatoid arthritis it may be wise to remove tonsils which are diseased and to treat active sinus infections not because of their proven etiologic relationship to the arthritis but because anything which improves the health of the patient will probably be of some benefit in overcoming the arthritis The decision regarding removal of a focus of infection must usually be made eventually by the internist after consultation with the laryngologist and the dentist

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STAPHYLOCOCCUS INFECTIONS

INTRODUCTION

STAPHYLOCOCCI are the commonest cause of pyogenic infections All forms of staphylococci except the *Staphylococcus aureus* are

relatively nonpathogenic By appropriate cultural methods however, and possibly in the human body the usually innocuous forms such as *S albus* and *S citreus* may be converted into the pathogenic *S aureus* Pathogenic strains produce a soluble toxin *leukocidin* a hemolysin a tissue necrotizing toxin plasma coagulase, and the so-called Duran Reynals factor,' an agent which enhances tissue permeability and infection Julianelle and his co workers have shown that staphylococci may be divided into types A' and 'B on the basis of immunologic and chemical differences between the intracellular polysaccharides elaborated by the respective organisms They found also that Type A strains ferment mannite and are pathogenic while the non mannite-fermenting Type B strains are not They demonstrated that the sera of patients suffering from prolonged general infection and of those finally recovering from infection contained precipitins for the specific carbohydrates It should be emphasized that strains of *S aureus* after eight to twelve hours incubation often appear almost white but develop the typical yellow pigment on exposure to the sun or to diffuse daylight

Although man is generally prone to staphylococcus infection there is a great variation in his susceptibility to the disease Trauma malnutrition agranulocytosis diabetes diseases of the kidneys and blood vessels filth friction of the skin and possibly variations in the acid reaction of the skin itself are important factors

Staphylococci are often found in symbiosis with streptococci pneumococci and influenza bacilli

While pure staphylococcus infection tends to remain localized at the site of entrance as in the skin sinuses middle ear tonsils teeth and lungs metastatic infection of the meninges heart pleura kidney bones joints and regional lymph nodes not infrequently occur and in severe infections the blood stream is invaded

HENRY T CHICKERING

FURUNCULOSIS

Definition.—Furunculosis is an infection of the skin characterized by the presence of multiple furuncles or boils appearing simultaneously or in successive crops

Etiology—Almost all furuncles are due to the entrance of *Staphylococcus aureus* into the hair follicles or skin

Symptoms—The individual furuncle may appear as a painful indurated elevated area of erythema which gradually increases in size for about four to seven days Then softening takes place and a small central yellowish spot appears which finally discharges pus This small opening enlarges until the softened slough can be evacuated after which healing rapidly takes place A boil may first appear as a very superficial infection about a hair follicle The vesicular head soon discharges and healing takes place or the infection may steadily penetrate into the deeper layers of the skin and go through the evolution just described If the boil is situated in an area where the skin is firmly attached to underlying fascia the lesion is clearly circumscribed and accompanied by pain If situated where the skin is freely movable there may be widespread edema of surrounding tissue and very little pain connected with the boil itself

Furunculosis usually develops through dissemination of the staphylococci discharged from the original infection to other parts of the body The prevention of this spread often presents great difficulty on account of the location of the original lesion in the axilla groin or vulva

Other factors such as malnutrition diabetes or conditions accompanied by itching contribute to one s susceptibility to staphylococcus infection Dirty fingers filth friction and contaminated clothing especially sweaters are important factors in the production of furunculosis

Morbid Anatomy—With the onset of infection there is a diapedesis of white blood cells to the infected area thereby localizing the infection In rare instances a single innocent looking boil may be followed by a general septicemia and death although usually the leukocyte reaction forms an effective barrier to a general infection Due to the production of soluble toxins and lytic agents a necrotizing action is produced in the center of the furuncle which leads to the formation of a slough composed of pus glandular and perifollicular tissue The slough grad

ually liquefies, separates from the surrounding tissue, and upon receiving sufficient drainage is evacuated and replaced by granulation tissue

Diagnosis —Usually there is no difficulty in the diagnosis The presence of pain and the subsequent evolution of the furuncle distinguish it from impetigo contagiosa Carbuncles are characterized by multiple points of suppuration whereas the furuncle has only one 'head"

It is important before incising a boil to examine microscopically a drop of the purulent secretion obtained by gently nicking the purulent spot (not squeezing) in order to establish the presence of staphylococci since early incision of an anthrax pustule greatly increases the danger of general dissemination of the infection and death

Prognosis —The prognosis in furunculosis depends a great deal on treatment The average duration of a single boil is one or two weeks but if care is not taken to prevent spread of the infection to new sites, it may run a prolonged course In rare instances general septicemia or pyemia may lead to a fatal termination

Treatment —The most important single factor in the treatment of furunculosis is to prevent dissemination of the infecting organism In severe cases the patient should be put to bed After a careful cleansing of the body, care should be taken not to rub the skin with a towel and separate towels should be used for drying the infected areas After the initial bath the tub or shower should be prohibited Often this procedure alone stops the succession of boils If the furuncles are localized in the axillae or on the perineum or vulva careful shaving with a sterile razor followed by a moist dressing of 1 5000 bichloride of mercury will protect the skin from reinfection Ethyl alcohol (15 per cent) or extract of hamamelis is often very effective Seventy per cent ethyl alcohol may be used for cleaning the oozing areas but its prolonged use as a dressing is irritating to some skins

As the boil matures a small opening may be made at the point of the suppuration taking care not to use force in expressing the contents and making as small an incision as possible to avoid opening of new avenues of infection The application of tincture of iodine into the sloughing area will assist in the separation of the slough Once the boil discharges the physician should exert all his ingenuity to prevent the spread of the infection The pus should be removed by patting with a sponge wet in alcohol not by rubbing If adhesive tape is used it should be removed by a solvent solution such as benzine to avoid abrading the skin and thus offering a new site for infection It is very important not to traumatize a furuncle situated on the nose or upper lip To do so may lead to a fatal bacteremia and meningitis It is in these cases that x ray therapy has proved very effectual

Staphylococcus aureus vaccine either stock or autogenous is sometimes of value in preventing the development of new furuncles Application to the skin of 5 per cent sulfathiazole or sulfadiazine ointment is also valuable in preventing fresh infections

HENRY T CHICKERING

CARBUNCLE

Definition —A carbuncle is an acute local inflammation of the deeper layers of the skin leading to the formation of multiple purulent openings and extensive slough

Etiology —The etiology of carbuncle is essentially that of a furuncle But due either to the special characteristics of the *Staphylococcus aureus* or to the lack of resistance of the patient, the infection spreads laterally through the skin producing a honeycomb like necrosis beneath the surface before the multiple purulent exits are formed

Pathology —The pathology of carbuncle is like that of furuncle in its incipiency It is not known whether the intense induration occludes the blood vessels of the area producing slough or whether certain strains of staphylococci produce hemolyzing and necrotizing substances in unusual abundance to effect this honeycomb type of slough Certain it is that in some cases where there appears to be every opportunity for free drainage from several surface exits the process continues to spread rapidly until the whole boggy purulent area is freed from the underlying fascia

Symptoms —The onset of a carbuncle may simulate a simple furuncle but often

constitutional symptoms such as fever chilly sensations and general malaise are more noticeable If a furuncle is traumatized by squeezing the area of induration may spread and become brawny and dark red in color, the infection spreading not only on the surface but deeper into the subcutaneous tissue After several days necrosis of the deep parts of the skin and the subcutaneous tissue takes place The skin itself thins out at several points showing yellowish red pus and finally a small amount of purulent fluid is discharged

The whole indurated area eventually becomes a mass of sloughing tissue which separates out, leaving a deep ulcer When complicated by bacteremia repeated chills and sweats ensue and death may take place

Diagnosis—Carbuncle differs from furuncle by its more extensive area of erythema and induration and by its multiple purulent heads Here again it is important to definitely rule out anthrax infection before instituting surgery

Prognosis—In the aged or debilitated or those suffering from diabetes or diseases of the kidneys and blood vessels the prognosis is always grave In such cases the occurrence of septicemia or septic embolic infections is not infrequently a cause of death

Treatment—The treatment is directed against the underlying constitutional condition as well as the local infection In diabetes measures to control the glycosuria and hyperglycemia should be vigorously instituted In those suffering from wasting diseases and anemia small repeated blood transfusions are useful In the milder carbuncular infections hot poultices of flaxseed or witch hazel often help to relieve pain and hasten the development of the multiple purulent heads When these simple measures are not followed by definite improvement free drainage should be instituted by a surgeon Usually this requires a crucial incision extending beyond the area of induration and a thorough freeing of the infected area from the underlying fascia During the past few years the results of x ray therapy in carbuncle have been very promising For about four hours after treatment there is increased swelling and pain followed shortly by marked decrease in symptoms The purulent heads coalesce and drainage becomes free In some cases a second or third exposure is necessary following which rapid softening of the infected area and healing takes place without surgical intervention

Henry T Chickering

STAPHYLOCOCCUS BACTEREMIA

(*Pyemia*)

Staphylococcus aureus bacteremia results when the staphylococcus is either constantly or intermittently circulating in the blood stream

Etiology—Where resistance to infection is low or the invasiveness of the particular strain of staphylococcus is high the blood conveys the germs from the local lesion to regions far distant from the primary focus Invasion of small numbers of bacteria from the focus are often taken care of and eliminated from the blood by the liver without metastatic infection But if the mass of infection is great or if the primary lesion is so situated that the lungs endocardium brain bones or urinary tract first receives the organisms metastatic abscesses frequently develop If the primary focus and the metastatic foci are properly drained the bacteremia clears up The continued presence of bacteremia indicates insufficient drainage

Morbid Anatomy—Infected emboli or free bacteria may be carried to any organ of the body and in staphylococcus infections multiple abscesses may develop Infection is prone to occur in regions whose blood supply has been damaged by previous infections as at the site of a chronic endocarditis Septic infections may develop on the heart valves as well as in the spleen kidneys or brain

Symptoms—The symptoms of staphylococcus bacteremia vary from a relatively mild febrile condition suggesting influenza tuberculosis typhoid or rheumatic fever to a very fulminating infection in which death supervenes in three days Occasionally an innocent looking pustule on the scalp or a furuncle on the nose or upper lip may terminate fatally in such a short time The fever may be intermittent or constant, often there are drenching sweats The blood usually shows a well marked polynuclear leuko

cytosis but occasionally in the fulminating cases white blood counts under 1000 and an almost complete absence of polymorphonuclear cells is seen

Staphylococcus meningitis may develop from an old chronically infected accessory sinus of the nose One patient whose symptoms on the first day suggested influenzal infection was dead four days later, the spinal fluid and blood showing pure *Staphylococcus aureus* infection In this case no primary focus was found at autopsy

When the endocardium is the site of the principal infection definite changes in the intensity and pitch of the heart murmurs are a very significant symptom In children staphylococcus pericarditis while uncommon, should always be borne in mind, for it is in these cases that brilliant results have been obtained from surgical drainage

Occasionally in furunculosis a small staphylococcus abscess may develop in the lungs It is often accompanied by localized pain, and recovery may take place without surgical intervention In other cases, a large lung abscess or an empyema may supervene and require surgical intervention

In staphylococcus bacteremia the possibility of perinephritic abscess should always be borne in mind If the kidney is the seat of septic emboli the presence of blood in the urine is a suggestive sign Infarcts of the spleen are accompanied by pain and palpable enlargement of the organ Metastatic infections of the eyes muscles and genitalia are rare though not infrequently the prostate is the seat of primary or metastatic infection The bones and joints are often implicated in *Staphylococcus aureus* infections Infection of the skin from scratching particularly in chickenpox may be followed by osteomyelitis of bones far distant from the site of the original furuncle Pain in the affected bone or joint and the presence of a healing furuncle suggest the diagnosis

Diagnosis—In febrile conditions the cause of which is not obvious the practice of making blood cultures is the most important aid in diagnosis Preferably the blood should be taken when the temperature is elevated Twenty cc should be removed from the arm vein and planted in plain broth and agar In this way an indication of the intensity of the bacteremia can be obtained Repeated cultures should be made if the first proves to be sterile The presence of *Staphylococcus aureus* in the blood rules out other infections, such as typhoid fever, rheumatic fever, pleurisy miliary tuberculosis, streptococcus endocarditis, malaria and trichiniasis

Prognosis—In fulminating *Staphylococcus aureus* infections the mortality rate is almost 100 per cent In less severe infections the death rate depends on the site of the metastatic lesions and whether adequate drainage can be obtained

Treatment—The treatment of staphylococcus pyemia is essentially surgical, although adequate sulfa drug therapy may prevent additional foci of infection Every effort should be made to secure satisfactory drainage If the infection has been of long standing or if the patient shows a secondary anemia of 60 per cent or more repeated small blood transfusions are helpful

Julianelle has recently reported on the treatment of staphylococcus bacteremia with a processed staphylococcus Type A rabbit serum with very encouraging results The careful bacteriologic and biochemical investigations on which this clinical study was based make the further use of this serum particularly desirable

Henry T Chickering

STAPHYLOCOCCUS AUREUS PNEUMONIA

Definition—*Staphylococcus aureus* pneumonia is an acute specific infection of the lungs characterized by the formation of multiple abscesses

Etiology—As early as 1889 Netter and later Fraenkel and Leichtenstern described an influenzal bronchopneumonia accompanied by the formation of abscesses from which the *Staphylococcus aureus* was isolated in pure culture

Infection of the lungs takes place by direct extension of the bacteria from the upper respiratory tract when conditions favorable to the growth of staphylococcus are present Strong support for this point of view is offered by the fact that bacteria found in the normal nose and throat such as hemolytic streptococcus pneumococcus *Haemophilus*

influenzae and others are occasionally seen growing in symbiosis with *Staphylococcus aureus* in this disease Moreover in *Staphylococcus aureus* pneumonia, metastatic infections in the bones joints and kidneys are most unusual in contradistinction to the picture seen in staphylococcus infections of the skin In staphylococcus pneumonia the disease spreads by direct extension instead of by the blood stream and lymphatics

The disease occurs most commonly in pandemics of influenza Chickering and Park reported 153 cases of postinfluenzal staphylococcus pneumonia in a series of 312 fatal cases as determined by postmortem lung cultures The disease also occurs endemically The author has seen 18 cases in private practice in a series of 500 cases of pneumonia of all types over a period of fifteen years Lyon has noted the disease in 9 6 per cent of cases of bronchopneumonia in children In 211 cases of primary atypical pneumonia Cole reported that 9 per cent were associated with *Staphylococcus aureus*

Morbid Anatomy—The primary catarrhal inflammation and edema of the respiratory mucous membrane with the tendency to hemorrhage into the walls of the bronchioles so characteristic of influenzal infection offers a favorable medium for the growth of the staphylococcus In the very fulminating infections lasting only five or six days from the onset of the influenza the lung shows such intense hemorrhagic infiltration that the cut surface resembles that of an acute splenic tumor If the disease is less acute multiple abscesses of all sizes depending on the duration of the disease are seen The distribution of the lesions is bronchopneumonic in character the dependent portions of the lung being most frequently involved There may or may not be any pleural exudate Examination of the surface of the pleura shows in addition to petechiae small yellowish white spots pinhead in size which prove to be minute abscesses The rupture of these subpleural abscesses is responsible for the frequent occurrence of single or multiple collections of pus in the pleural cavities Where the disease has lasted seven or more days the cut surface of the lungs shows myriads of minute abscesses some coalescing to form larger foci Microscopic sections of the lung show intense congestion with rupture of the alveolar walls and exudation of serum and red cells into the alveoli When stained for bacteria typical clusters of gram positive cocci are seen

Symptoms—The onset of *Staphylococcus aureus* pneumonia is almost always insidious and rarely accompanied by the chill and localized pain of lobar pneumonia If it develops as a complication of influenza the temperature rises instead of disappearing by the fourth day and the patient becomes gravely ill The expression is anxious and a peculiar cherry red cyanosis develops At this period signs of pulmonary involvement are extremely scanty perhaps nothing more than slightly decreased resonance and diminished breath sounds at the bases and a few fine moist rales Herpes labialis is uncommon The mind remains surprisingly clear throughout the disease

Occasionally pleuritic pain is complained of but this is not usual In the latter stage of the disease profuse sweating may take place The fever on the whole is high ranging between 104° and 106° F with frequent remissions The pulse is relatively slow at the onset and in only a few cases does it rise above 120 until just before death The quality of the pulse is usually small and weak Respirations range between 24 and 36 and in some cases rise to 50 or 60 without much apparent discomfort

The severity of the symptoms may increase with the most startling rapidity and death may follow in two or three days the signs in the chest being those of a patchy bronchopneumonia Of the cases seen in the influenza pandemic of 1917 12 died between the first and fifth day and 73 between the sixth and tenth day A few cases live to develop large pulmonary abscesses and suppurative pleurisy

Diagnosis—The sputum in staphylococcus pneumonia unlike the rusty tenacious material of pneumococcal infections is often friable purulent and of a dirty *salmon-pink* color Typical sputum however is not always obtainable and the patient may produce only greenish yellow purulent material which on direct smears and cultures shows the staphylococcus as the predominant organism

If sputum containing the staphylococcus is streaked on glucose free blood agar plates

the colonies appear as opaque round, shiny disks surrounded by a wide zone of hemolysis after eighteen hours' incubation On removal from the incubator, the colonies may appear white, but if the plates are allowed to remain a few hours in sunlight the yellow pigment appears

In the severe cases the staphylococci invade the blood stream, about 50 per cent of the writer s patients had positive blood cultures In spite of the high percentage of blood cultures only one patient developed meningitis In most cases of staphylococcus pneumonia death takes place before complications have an opportunity to manifest themselves In the few that survive staphylococcus empyema pericarditis and massive lung abscess are the common sequelae

Many cases of staphylococcus pneumonia show a marked leukopenia This may be due to the influence of the primary influenza infection for it has been noted that where the disease is less severe and of longer duration a well marked polymorphonuclear leukocytosis is present

The x ray is of great assistance in demonstrating the scattered patchy areas of bronchopneumonia and the presence of fluid in the pleural cavities or the pericardial sac

Prognosis —The mortality rate in *Staphylococcus aureus* pneumonia is extremely high (from 70 to 80 per cent die in the acute phase of the disease) although increasing experience with the use of sulfonamides has made the prognosis less grave In a few cases small lung abscesses demonstrable by x rays resolve without surgical intervention More often there eventuates a staphylococcus infection of the pleura or pericardium which yields to adequate surgical drainage

Treatment —Although treatment of the fulminating cases of *Staphylococcus aureus* pneumonia is usually ineffectual several observers have reported good results from the use of sulfathiazole and sulfadiazine In addition the anti staphylococcus Type A rabbit serum of Julianelle should be used if available Recently a few cases treated with penicillin have been reported with astonishingly good results The oxygen tent may aid in tiding the patient over the acute stage of the disease Surgery may be necessary in the cases which develop empyema although five of six cases of Finland treated with sulfa drugs required only repeated aspirations

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GONOCOCCAL INFECTIONS

Definition —The term gonococcal infections designates maladies which have a common etiologic basis but are diverse in their clinical manifestations The individual signs and symptoms of the several diseases caused by the gonococcus (*Neisseria gonorrhoeae*) are varied and depend to the greatest extent upon the locations in the body of the offending infection The numerous clinical entities are identified therefore by reference to the tissues or organs which are principally involved

Historical —The gonococcus first of the group of gram negative cocci to be described was identified in 1879 by Neisser who observed its special characteristics in urethral pus Artificial cultivation being difficult, however the *significance of the species in the etiology* of diseases of general medical interest (other than genital infections) did not become firmly established on a sound bacteriological basis until a decade or more later In 1893 Rendu first cultivated the organisms from exudates derived from acute arthritis Thayer and Blumer in 1897 first isolated gonococci antemortem from the blood stream of a case of endocarditis

Within the scope of gonococcal infections encountered in internal medicine the following is a list of diseases which have been described and which have been proved or have been considered on reasonable grounds to be of neisserian origin

1 Arthritis bursitis tenosynovitis myositis osteitis periostitis, chondritis perichondritis
2 Endocarditis pericarditis, myocarditis (abscess formation), thrombophlebitis
3 Cutaneous manifestations hyperkeratosis simple erythema erythema nodosum pustular bullous and hemorrhagic exanthemata condylomata, keratodermia blennorrhagicum
4 Meningitis myelitis meningomyelitis polyneuritis sciatica psychoses and neuroses
5 Laryngitis tonsillitis otitis media adenitis pneumonia (usually embolic) parotitis thyroiditis
6 Acute glomerular nephritis, pyelonephritis and pyonephrosis
7 Proctitis and peritonitis
8 Septicemia and infected surgical wounds

(Ophthalmic and genito urinary diseases are not included)

Etiology—The gonococcus belongs to a group of micro organisms classified as Neisseria The two members of the group most commonly encountered in infection in man are *Neisseria gonorrhoeae* (gonococcus) and *Neisseria meningitidis* (meningococcus) A third member *Neisseria catarrhalis* is rarely important in the production of disease However since it is a common inhabitant of the upper respiratory tract differential bacteriologic diagnosis may be important in determining the cause of diseases where cultures of nose throat or sputum are employed

Members of the Neisseria group are gram negative cocci which are commonly seen in pairs (diplococci) Morphologically they are characterized by the fact that the adjacent sides of the oval pairs are flat or concave in contrast to the elongated structure of other diplococci such as pneumococcus The oval form with flat abutting sides is so typical that they have been commonly described as biscuit shaped or kidney shaped diplococci In these shapes and contained within leukocytes they are most commonly seen in stained smears of exudates derived from patients

The gonococcus is an aerobe (usually obligate) and is relatively fastidious in the growth requirements necessary for artificial cultivation They grow poorly or not at all in plain meat infusion broth or agar Of numerous media advocated those to which some protein of the body is added such as serum or ascitic fluid usually serve as the most satisfactory The use of atmospheres containing increased per cent of CO_2 has been advocated by some bacteriologists However others have failed to confirm this finding and refer to factors relating to pH and degree of humidity and prevention of evaporation as possible important elements which require control in evaluating the significance *per se* of the CO_2 concentration of the media

Each of the three gram negative cocci just discussed is with greatest frequency derived from three different sources in the body (*N gonorrhoeae* from genito urinary tract *N meningitidis* from cerebrospinal fluid and *N catarrhalis* from nasopharynx) Consequently the source of the material from which these morphologically indistinguishable organisms are derived is usually reliable evidence for differentiation However errors in etiology have been made because absolute differentiation has not been accomplished This is particularly well illustrated by the fact that the conjunctivae and also the joints may be infected either with the gonococcus or the meningococcus and if other clinical evidence does not point to the nature of the infection complete bacteriologic identification of the organism isolated from the lesion is necessary

Pathogenesis—The portal of entry of gonococcal infections is except in unusually rare instances the genito urinary tract both in males and females The manifestations observed in medical clinics are therefore secondary to the original local infection and are in the strict sense complications of the primary gonorrhea The transport of the organisms from the initial focus to other tissues of the body is most often accomplished by spread to structures adjacent to the inflammation or by lymph channels to inguinal and other region lymph glands However for internal medicine the metastasis of gonococci usually occurs by way of the blood stream In this connection it is an interesting fact that the transfer of the organism to remote parts of the body as

the joints, is not characterized by the stormy clinical course of bacteremia but is in most instances silent since the period between the gonorrhea and the clinical appearance of gonococcal diseases may be one of com parative good health

In pathologic material there is no typical pathognomonic histologic or cytologic pic ture by which the gonococcal nature of in flammation may be diagnosed Demonstra tion of the presence of gonococci in the lesions is necessary

Endocarditis—The clinical picture of en docarditis which follows the implantation of gonococci on the heart valves is closely simi lar to bacterial endocarditis caused by *Streptococcus viridans* or some other bac terial species In addition to the cardiac find ings characteristic of endocarditis other manifestations which are commonly encoun tered consist of fever anemia petechiae embolic phenomena (lungs spleen brain etc), nephritis arthritis and others Leuko cytosis is usually well marked Secondary anemia develops rapidly In the heart itself two features of special interest are the se lective valvular involvement and the fact that preexisting valvular disease (rheumatic endocarditis or congenital abnormality) is not a prerequisite for gonococcal valvulitis Damage to the valves existing prior to the occurrence of gonococcal endocarditis has been noted in only 15 to 20 per cent of cases The aortic valves are most frequently at tacked but the valves of the right side of the heart are also the special site of gono coccal localization, occupying the second place in point of frequency of involvement Since the pathologic lesions are destructive and ulcerative the character of the mur murs is likely to change in quality and intensity as the disease progresses Suppura tive myocarditis may occur as a result of ex tension of the infection from the valves Pneumonia may follow the implantation of infected emboli in the lungs

The development of endocarditis coinci dent with the early acute phase of an initial attack of urethritis is rare The valvular dis ease occurs at a later date, ranging from two to six weeks after the beginning of gonorrhea In many instances the relation ship between the onset of genito urinary infection and endocarditis cannot be estab lished The diagnosis of gonococcal endo carditis, when suspected, is substantially aided by determining the presence of gono cocci in the genital tract even though a history of gonorrhea has not been obtained When genito urinary discharge is absent, ex amination of prostatic material following massage or cervical smears in the female are helpful and important procedures

Gonococcal endocarditis usually runs a more malignant course than that of endo carditis due to *Streptococcus viridans* the average duration of the former being five to nine weeks The course is progressive, and spontaneous remission is a great rarity Gonococcal infection may be suspected in a case of severe endocarditis with definite signs of valvular disease of the right side of the heart However the etiology can be established only by blood culture Failure to obtain gonococci from the blood stream is not an uncommon experience The unsuc cessful attempts are accounted for by dif ficulty in cultivating gonococci particularly when the size of the inoculum as repre sented by the number of organisms in 5 to 10 cc of blood may be small An additional contributing factor may be ascribed to the right sided cardiac lesion with the capil lary bed of the lungs serving as a filter before the organisms reach the general cir culation

Recovery has been reported in a few authentic cases The mortality is approx imately 95 per cent In several of the re ported cases which have recovered the course of the disease has been prolonged and subacute rather than progressively and con tinually acute in character

Arthritis—Arthritis constitutes the most common form of gonococcal infection en countered in internal medicine In the major ity of cases it presents itself as an acute febrile illness in which inflammation of the affected joints is readily apparent Although reports vary considerably arthritis probably occurs as a complication of gonorrhea in about 3 per cent or less of the cases It develops secondary to genital gonorrhea and most frequently follows the initial infec tion from one to four weeks However the interval may be longer or indeterminate Because of the fact that urethritis in males may be mild and that cervicitis in females

may be unnoticed a history of recent gonorrhea may not be obtained Direct examinations of urethral discharge or prostatic secretions or cervical exudate are important diagnostic procedures in establishing the presence of a primary focus In cases of chronic gonococcal infection of the genitourinary tract inciting causes such as trauma and others the nature of which is not understood may cause arthritis to develop without a recent acute exacerbation of the original local infection Neither the severity of the arthritis nor its incidence is dependent upon the severity of the preceding attack of gonorrhea

The onset is usually acute and accompanied by a general reaction with malaise and fever The course of the temperature during the acute period is characterized by a moderate degree of fever which runs an intermittent course and gradually subsides as the inflammatory reaction lessens Polymorphonuclear leukocytosis develops with average counts ranging from 9000 to 15 000 white blood cells Anemia does not develop unless improvement is delayed for a considerable period of time or unless the preceding gonorrhea was debilitating

Pain is a prominent symptom which in the early stages may be widespread among many joints As the acute process progressively develops involvement of one two or several joints becomes conspicuous with swelling local increased heat and redness The pain may become unusually intense and overshadow the earlier polyarthralgia Limitation of motion and muscle spasm are characteristically present

Although the monarticular nature of gonococcal arthritis has been frequently emphasized it is usually polyarticular and its distribution is predominantly among a few of the large joints Knees and ankles are most commonly affected followed in frequency by wrists elbows shoulder and hip joints In a small number of instances the infection may be limited to one of the less commonly involved joints such as the sternoclavicular or temporomaxillary The small joints of the hands or feet may also bear the brunt of an attack or their involvement may accompany that of larger joints

Fluid accumulates within the joint capsule and periarticular swelling is also present The exudate aspirated from inflamed joints is turbid due chiefly to polymorphonuclear leukocytes The number of white blood cells usually in the tens of thousands ranges from 1000 or 2000 to over 50 000 Myers Keefer and Holmes have attached prognostic significance to the total cell count When the number of cells was greater than 40 000 chronic disability usually resulted whereas in cases in which the counts were less than 40 000 complete recovery more regularly occurred

The correct diagnosis is established by demonstrating gonococci in the fluid The organisms are not found in great abundance Careful and prolonged search of centrifuged material may be necessary In many instances no gonococci are identified Cultures may reveal gonococci when direct examination is not informative Both measures may be negative Myers Keefer and Holmes believe that organisms are most likely to be present when the synovial membrane is destroyed by the intense inflammatory reaction When organisms are not present the inflammation is confined beneath the surface of the synovial membrane The demonstration of gonococci in fluids makes a somewhat worse prognosis but does not conclusively point to permanent disability since many exceptions may be encountered

The final outcome of gonorrheal arthritis is very varied Complete and permanent recovery most frequently occurs Arthritis may assume a chronic form that endures with limitation of motion long after the acute process has subsided The chronic condition may gradually improve or it may become progressively worse and result in ankylosis and permanent disability

Acute suppurative tenosynovitis may occur without arthritis and has been observed to follow trauma or involve tendons used in the patient s occupation

The so called gonococcal heel observed occasionally in association with arthritis is dependent upon periostitis of the os calcis with the development of an osteal pur Patients with this complication complain of pain in the affected heel particularly as a result of pressure Roentgenographic examination reveals an exostosis

Cutaneous manifestations occur in association with other active neisserian infections either of the genito urinary tract and adnexa or with metastatic diseases The numerous disorders of the skin are not in themselves typical of gonococcal infection with the exception of *keratodermia blennorrhagicum* a somewhat rare disease which should only be diagnosed in association with the presence of proved gonococcal disease

Meningitis and other involvements of the central nervous system are rare but occur as metastatic infections from active genital ophthalmic or endocarditic lesions Primary gonococcal meningitis has also been described Since the gonococcus and meningococcus are morphologically identical the true nature of the disease may not be recognized in sporadic cases of meningitis unless biologic identification of the strain is made

Nephritis —Proven cases of gonococcal nephritis are not common Pyelonephritis and pyonephrosis are encountered in cases of active disease of the lower urinary tract following extension of the infection upward Clinical and laboratory signs of renal insufficiency are present Surgical treatment is often required in order to promote drainage of the infection and impede further extension Acute glomerulonephritis may occur during the course of endocarditis It also has been noted in association with other active gonococcal infections Renal insufficiency develops and may be followed by uremia

Septicemia refers to the persistent presence of gonococci in the blood stream in sufficient numbers or of such a degree of toxicity that the general reaction is marked and the clinical course stormy Septicemia associated with acute primary gonorrhea is unusually rare A septic bacteremic course with metastatic infections and embolic manifestations may occur in any of the types of gonococcal infection Gonococci are recovered from the blood stream most frequently in cases of endocarditis

Diagnosis —In the early acute stages of polyarthritis the differential diagnosis between acute rheumatic fever rheumatoid arthritis other types of infectional arthritis and gonococcal arthritis is often not possible on clinical grounds The following are practical points in the diagnosis of gonococcal infections

1 History of gonorrhea, by name or symptoms Latent gonorrhea of long duration as well as a recent attack may serve as the focus from which metastatic gonococcal infections arise

2 Examination by stained smear and by culture of inflammatory exudates from lesions (joint fluids etc), for typical gram negative gonococci usually intracellular Blood cultures should be made

3 Examination for gonococci by stained smear of material derived from the genitourinary tract, viz urethra prostate seminal vesicles and draining inguinal lymph nodes in males and Bartholin's glands vagina cervix in females

Even at times of active disease the demonstration of gonococci may be difficult or even repeatedly unsuccessful Consequently, the diagnosis may not be completely proved and it becomes necessary to institute special therapeutic measures on the basis of the presence of characteristic clinical features and additional suggestive laboratory data

Complement fixation Test —When performed with properly prepared reagents the test is a valuable aid in diagnosis The reaction may not become positive until several weeks after the beginning of infection Consequently, if the result is negative but suspicion of gonococcal infection is strong repeated tests should be made at weekly or bi weekly intervals The fixation test may remain positive for many months This latter fact may be a source of error in diseases unrelated to gonococci which appear in patients who have had gonorrhea at some previous date In general a positive complement fixation test is more valuable than a negative one

Roentgenographic Changes —Early in acute arthritis the articular and periarticular swellings are noted but cartilage and bone appear normal Following complete recovery no abnormality persists When chronicity develops and damage to tissues of a joint has occurred evidence of destruction of cartilage is evident Subsequently if the disease progresses thinning of bones is noted due in part to disuse Finally ankylosis is noted particularly in joints the

articulating surfaces of which are normally in close approximation as hip ankle and wrist

Treatment —Compounds of the *sulfonamide series* are of great value in any type of gonococcal infections Sulfanilamide has proved its usefulness but it seems likely that other compounds such as sulfathiazole or the less toxic sulfadiazine are more effective

A second mode of treatment helpful in general in gonococcal infections is *fever therapy*

The literature has not yet revealed the outcome of a large series of cases of *gonococcal endocarditis* treated with the sulfonamide compounds although a few individual favorable reports have been made and the drugs should be employed as soon as possible Fever therapy induced either with hyperthermic apparatus or with intravenous typhoid vaccine has also been advocated in combination with chemotherapy The difficulties inherent in the treatment of any bacterial endocarditis are particularly applicable to the gonococcal type Consequently it is the least successfully treated of the gonococcal infections Either or both of the measures mentioned warrant trial in this highly fatal disease

Gonococcal arthritis responds well to chemotherapy In early acute cases 80 per cent recovery or marked improvement has been reported from some clinics Using sulfanilamide Bauer and associates and Culp and Cobey point to the particular success when treatment is instituted before damage to the joints has occurred The same authors also recommend that the level of sulfanilamide in the blood should be maintained at 8 to 10 mg per cent or higher The size and spacing of doses of the drug have varied in different clinics Total daily doses of 4 to 8 Gm divided into 1 to 2 Gm per dose given at intervals of three to six hours constitute the range of treatment most commonly advocated for adults of average size

Although the reports mentioned deal with sulfanilamide for treatment sulfathiazole and sulfadiazine have been found to be more potent against gonococci Consequently either of the latter compounds preferably sulfadiazine appears to be the drug of choice at the present time The course of treatment is essentially the same irrespective of the sulfonamide compound selected for use Recent reports indicate that certain gonococcal infections which do not respond to sulfonamide therapy are quickly controlled by the intravenous administration of Penicillin Within recent years fever therapy has found a valuable place in the treatment of gonococcal arthritis In obstinate cases that do not respond to sulfanilamide hyperthermic treatment offers an additional advantageous method Repeated application of dry heat to the affected joints is a helpful adjunct Splinting of the affected joint is often of great assistance in alleviating pain The splints should be applied with the joints extended in the approved orthopedic position Eradication of the primary genitourinary infection is desirable either by the use of sulfonamide drugs or by topical applications and irrigations However massage and instrumentation should be used with conservatism since local irritation may cause the metastatic disease to flare up

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MENINGOCOCCAL INFECTIONS

CEREBROSPINAL FEVER

(*Spotted Fever Epidemic Cerebrospinal Meningitis Meningococcus Meningitis*)

Definition—Cerebrospinal fever is an infection with the *Diplococcus intracellularis* which occurs sporadically or in epidemics It is characterized by primary local involvement of the nasopharynx or tonsils, secondary invasion of the general blood stream, and metastatic inflammation of the meninges and more rarely of other parts of the body

History—To Vieusseux of Geneva, and to Danielson and Mann of Manchester Massachusetts belongs the credit of the earliest and independent descriptions of this disease in 1805 and 1806 In 1811 North of New York published the first monograph on the subject To Jochmann in Germany and Flexner in the United States belongs the credit of establishing serum therapy

Incidence—Sporadic cases are almost always present in any large community At irregular and infrequent intervals epidemics occur These most often arise where individuals are crowded together in new or unsanitary surroundings as in army camps jails and other institutions Nevertheless as in New York in 1905 epidemics may arise without peculiar circumstances

Etiology—The *meningococcus* was identified as the cause of meningococcus meningitis by Weichselbaum in 1887 It is a gram negative diplococcus almost strictly parasitic for man and can be grown on artificial media only if animal protein is present Toxins appear to be both intracellular and extracellular, and phagocytosis is a dominant factor in immunity Several varieties or types of the organism are described In England and the United States these number four Types I II and III are more or less well defined immunologically Type IV or 'X' comprises all organisms outside the other groups It is important to recognize that serum which is active against one type may be inert against another Apparently the disease is almost solely transmitted by 'droplet' infection from the mouth or nose of the carrier Carriers are always present in a community and may be individuals suffering from the disease or in the incubation period or chronic or casual carriers

Morbid Anatomy—During meningitis there is intense congestion, often with punctate hemorrhage in the dura In its earliest stages the disease is revealed by congestion of the pia arachnoid and choroid plexus with localized infiltrations of round and polymorphonuclear cells and erythrocytes The exudate typical of the later period of the meningitis lies between the arachnoid and the pia mater, is composed of leukocytes fibrin meningococci and red blood cells and may be thin and milky or lie in thick greenish yellow masses about the base or distributed along the sulci of the cortex and throughout the ventricles In prolonged cases with internal *hydrocephalus* or block the site of obstruction may be evident in the region of the roof of the fourth ventricle the aqueduct the foramina of Monro or in the spinal subarachnoid space The brain is compressed and flattened and the ventricles distended In some acute cases the brain stem may be forcibly wedged in the *foramen magnum*

Insufficient attention has been paid to the *encephalitis* accompanying the infection Perivascular foci made up of round cells pus cells red blood corpuscles and meningococci may be found throughout the encephalon Macroscopic areas of hemorrhagic or purulent character may also be found Changes in the spinal cord and its coverings similar to those found in the cranium may be seen Intracranial hemorrhage is not infrequent

Pericarditis endocarditis arthritis pneumonia pleurisy empyema panophthalmitis empyema of the accessory nasal sinuses epididymitis peritonitis and adrenal hemorrhage all may occur and indicate the widespread invasion of the host by the *meningococci* Petechial hemorrhages may be seen on all serous surfaces

Symptoms—The infection may be divided into 3 stages the first a local infection of the upper air passages the second a general invasion of the blood stream or stage of *meningococcus* sepsis the third a stage of metastatic localization usually in the meninges not infrequently in joints pericardium endocardium lungs skin and other regions These 3 stages may merge and coexist

The *first* or *carrier stage* may exhibit no symptoms other than the local presence of

meningococci or there may be tonsillitis pharyngitis sinusitis or conjunctivitis with moderate purulent discharge containing the characteristic diplococci

The *second stage* is one during which the organisms are dispersed by the blood stream from the initial focus in the upper air passages Under appropriate conditions as in military organization or closely observed epidemics this stage can be readily recognized by the following features the patient is dull apathetic indifferent he plaintively resents disturbance responds in monosyllables with the expenditure of a minimum amount of energy and prefers to lie on the side with knees drawn up and head bent forward There is no modulation of voice or play of expression Silence and immobility are striven for and active delirium or coma is infrequent This striking deviation from the normal mentality at once arrests the attention of the experienced observed The oral secretions are dry and viscid and moderate cyanosis or ashen pallor is common In 300 cases the initial temperature averaged 101° F Slight chills are frequent The pulse is rapid There is complaint of being sore all over and arthralgia or a mild polyarthritis often occurs The deep reflexes are exaggerated and may be unequal There is hyperesthesia

The most distinctive feature is the *rash* which consists typically of a capillary hemorrhage into the skin and mucous membranes In size the spots vary from a pinpoint to irregular areas 0.5 inch in diameter They are dusky red do not vanish on pressure and fade within three or four days leaving a rusty stain *Purpura* is a feature of the fulminating cases Milder prolonged types exhibit a maculopapular rash resembling the roseola of enteric fever except that the individual spots are larger Bleb formation often followed by local gangrene has been described *Gangrene* of the toes or of an entire extremity is rarely seen The leukocyte count is constantly increased numbering from 15 000 to 60 000 with an average polymorphonuclear percentage of 90

In this stage meningeal symptoms and signs are absent The *spinal fluid* is clear and has a normal cell count it may or may not contain an increased quantity of globulin and an occasional extracellular diplococcus The nasopharynx the skin lesions or the blood stream may reveal *meningo*

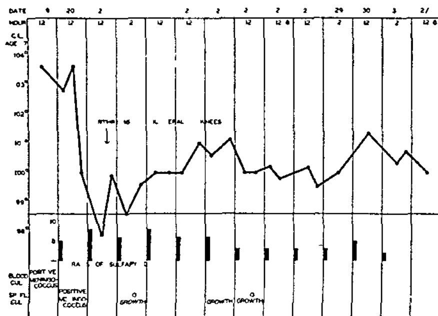


Fig 19 —Temperature chart of a forty-seven year-old chauffeur (C L) who came into the hospital in the premeningitic stage The following morning developed rash stiff neck, stupor Treated with 58.5 Gm of sulfapyridin over a period of thirteen days Improvement very rapid in the next three or four days Temperature curve affected by meningococcus arthritis of both knees which developed on the third day

cocci provided appropriate methods of cultivation are used This stage of sepsis may last a few hours or many days or weeks Rarely the third, or metastatic stage does not occur at all

The *third* or *metastatic, stage* is ushered in by a bursting headache, vomiting, chilly feelings and fever, frequently, in children with delirium and convulsions The patients exhibit retraction of the head stiffness of the neck, positive Kernig s and Brudzinski s signs, a relatively slow pulse, often with vagus irregularities and the *tache cerebrale* As the course of the temperature is erratic no typical chart can be drawn There may be quotidian or tertian rises, with intervening remissions or intermissions Afebrile periods lasting for hours or days may be followed by renewals of fever, often with chills Prolongation of fever beyond the seventh day suggests that treatment is inefficient that some complication has arisen or that serum sickness has developed With increased intracranial pressure the veins of the forehead may become distended and the respiration be of the Cheyne Stokes Biot or undulatory type Insomnia, delirium and coma may occur

In the early stages the pupils are dilated later, irregularities appear and a varying *strabismus* from irritation or paralysis of the oculomotor nerves is frequent Other rarer findings are fulness of the retinal veins retinal edema, hemorrhages or with internal hydrocephalus papilledema Blindness of central origin may occur but is rarely permanent Herpes of the lips or face is one of the commonest signs It is rarely seen before the fifth day and seldom leaves scars In infants bulging of the fontanels is an important sign The leukocytosis of the early stages continues Meningococci have been demonstrated in the leukocytes of the ordinary stained blood film Positive blood cultures can be obtained in from 5 to 80 per cent of cases but are most often found in the premeningitic stage when special technic is employed Except for the initial vomiting the gastro intestinal tract is not involved An epididymitis of benign course and outcome may occur in some epidemics Retention of urine may be overlooked Bronchitis and broncho or lobar pneumonia may occur at the onset or as a complication

In the *fulminating type* there is an overwhelming general toxemia with predominant hemorrhagic skin lesions The temperature may be subnormal or unusually elevated. Death may occur a few hours after onset. Petechial spots of all sizes and diffuse purpura are typical Differentiation from the hemorrhagic types of the exanthemata may be possible only on epidemiologic or bacteriologic grounds Meningitis may not occur The blood culture is practically always positive

Atypical meningococcic infections are not uncommon These may be manifested by prolonged, irregular fever, with arthritic symptoms petechial or maculopapular rashes, enlargement of the spleen a positive blood culture, and extrameningeal foci of infection Meningitis may not occur or may appear after many weeks of general symptoms

In no acute disease is the course more variable Recrudescence and relapses are present in 20 to 30 per cent of cases In rare instances there have been several attacks within two years Among the *complications* are purulent conjunctivitis panophthalmitis transitory amaurosis rarely optic neuritis and retinitis Otitis media is common Deafness following involvement of the eighth nerve is usually permanent Pericarditis and vegetative endocarditis occur The blood pressure is low in the stage of sepsis, but with increased intracranial pressure in the later meningitis or block it becomes elevated An acute arthralgia or polyarthritis is often an initial symptom and an erroneous diagnosis of *purpura rheumatica* may be made As a late complication a purulent monarthritis usually of the knee may occur The prognosis in such cases is usually good A third type of arthritis is the effect of serum therapy and may occur seven or more days after beginning the treatment

Internal Hydrocephalus or Subarachnoid Block.—Most common in infants this most serious complication arises from organization of exudate in the system of channels through which the cerebrospinal fluid circulates The subarachnoid block may occur at the roof of the fourth ventricle at the sites of the foramina of Luschka and Magendie in the aqueduct of Sylvius the foramina of Munro or even in the spinal subarachnoid

space The symptoms may be acute with unbearable headache cyanosis of the face and fulness of the veins of the forehead and retina delirium and not infrequently, sudden death—at times following lumbar puncture or chronic with weeks of rapid emaciation clouded mentality enhanced meningeal irritability, ocular palsies and eventual death Unless relieved by drainage hydrocephalic meningitis is always fatal

In the early stage of infection when there are symptoms of generalized disease the *cerebrospinal fluid* may be altogether normal and may remain so for hours days or in rare cases weeks or throughout As secondary meningitis develops isolated organisms may be found later globulin an increase in the number of mononuclear and then polymorphonuclear cells When the cell count is more than 400 per cubic millimeter the fluid becomes cloudy, later it may be *made very thick with pus cells fibrin and* meningococci The latter are found largely within the pus cells and are comparatively infrequent in most cases In general the presence of a large number of organisms suggests ome other form of meningitis Occasionally the spinal fluid is very thick and coagulates on standing Blood may be present as the result of the needle puncture or of rupture of the ependymal veins Dry taps may result from block from clogging of the needle by too thick exudate from faulty technic or without apparent cause As the infection subsides the cerebrospinal fluid becomes clear contains less protein fewer cells a large proportion of lymphocytes and fewer organisms or none at all In some of the prolonged cases the fluid may become clear but is under increased pressure contains a slightly increased number of cells and usually no organisms—the picture suggesting a hypersecretion Shortly after the onset of meningitis *meningococci* can be recovered from the cerebrospinal fluid by culture with little difficulty After serum treatment is under way it is very difficult to obtain a positive culture A safe clinical rule is to proceed at once with antimeningococcic serum or chemotherapy whenever a febrile condition is accompanied by a cloudy cerebrospinal fluid even when organisms cannot be found In infants irritability drowsiness stupor or coma vomiting convulsions muscular rigidity, increased tendon reflexes bulging fontanel and hemorrhagic rash and irregular respiration invite attention to the possibility of this disease

Diagnosis —Although sporadic cases are common the presence of an epidemic is an important factor Meningitis may exist concurrently with other infections The premeningitic stage may be recognized by the slight fever the peculiar manner attitude and facies the cutaneous vasomotor disturbance or the typical rashes the marked leukocytosis with polymorphonuclear increase the heightened and ill balanced activity of the reflexes the presence of infection in the upper respiratory tract the general aching and soreness or arthralgia and by the demonstration of meningococci in the nasopharynx by blood culture or in the thoroughly centrifuged cerebrospinal fluid With the onset of definite meningeal symptoms *diagnosis is rarely difficult and the evidence* obtained by lumbar puncture is almost always decisive

Meningismus —In the *acute infections* particularly in childhood symptoms of meningeal irritation may be very prominent and confusing Scarlet fever influenza typhus fever pneumonia mumps gastro enteritis and tonsillitis may be attended by headache vomiting stiffness of the neck and positive Kernig s signs During these diseases however the cerebrospinal fluid is clear and rarely contains an increased number of leukocytes Fifty or more cells per cubic millimeter may be present but the fluid does not become purulent and the development of the original disease makes the picture clear In the differentiation of influenza and typhoid fever from meningococcic infection the lack of leukocytic increase in the blood in both these diseases is decisive While the maculopapular eruption so common in typhoid fever is occasionally seen in meningococcic infections the longer incubation period the longer more regular course with abdominal symptoms the more uniform picture and the positive bacteriologic or serologic evidence of typhoid provide means of differentiation

Sepsis with meningeal or cerebral metastasis may give a confusing picture The portal of entry the frequent involvement of the endocardium the bacteriologic evi

dence obtained from blood culture and from direct examination of the spinal fluid usually serve for differentiation The petechiae accompanying the common types of streptococcic sepsis are much smaller than the hemorrhagic spots seen in meningococcus infection The cerebral form of poliomyelitis *in contrast with meningococcic meningitis* often begins with symptoms of a gastroenteritis The temperature is higher at the onset and declines more promptly while herpes and hemorrhagic eruptions are absent and the evidence of meningeal irritation is usually less The spinal fluid shows a higher proportion of lymphocytes and the bacteriologic evidence is, by ordinary methods negative The reflexes are usually diminished and paralysis is common *Tetanus* may be differentiated by the paroxysmal character of the attacks—the trismus, the history of a wound the absence of headache and the lack of pus cells in the cerebrospinal fluid In *tuberculous meningitis* the history of similar infection in the family, the slower onset the evidence of tuberculosis elsewhere in the body the absence of hemorrhagic rashes and of marked leukocytosis rarely the finding of choroidal tubercles the lesser increase in the number of cells in the spinal fluid and the presence of tubercle bacilli usually serve to clear up the problem

Septic meningitis caused by the common pyogenic organisms is usually secondary to a focus in the middle ear the accessory nasal sinuses scalp or face Organisms are usually abundant in the cerebrospinal fluid which becomes rapidly thickened by pus and the course is usually very short and fatal Other conditions which are rarely confused with meningococcus meningitis are *delirium tremens rheumatic fever* with cerebral involvement *subarachnoid hemorrhage diabetic coma uremia tetany* and *cerebral abscess hemorrhage* or *thrombosis*

Prognosis is extremely difficult and one can never safely predict what is going to happen in a given case of meningococcus infection The general mortality rate before the introduction of sulfonamide therapy was very high averaging about 50 per cent for the country at large This unfortunately was true in spite of the fairly widespread use of antimeningococcus serums However in a number of selected hospital series of cases properly treated with type specific serum, the case fatality rates were as low as those recently obtained with sulfonamide drugs The mortality in cases properly treated with sulfanilamide* and particularly with its later derivatives sulfapyridine sulfathiazole and sulfadiazine should not exceed 5 to 10 per cent The lowest mortality rate is obtained when treatment is begun on the first day of the disease and the rates rise according to the time which has elapsed between the onset of the disease and the time treatment is begun In the acute fulminating cases with extensive purpuric eruption and adrenal and other visceral hemorrhage (Waterhouse Friderichsen syndrome) death usually occurs within twelve to forty eight hours of the first symptom, and in spite of intensive treatment Age is still an important factor the highest mortality rates occurring less than the age of three and in those more than fifty years old Failure to respond promptly to treatment is ominous and this is equally true of serum and of sulfonamide therapy Patients with hydrocephalus or endocarditis seldom recover, although death may be delayed in cases treated with sulfonamide Early arthritis usually responds rapidly to chemotherapy The occurrence of cranial nerve involvement is serious With general recovery however involvement of most of the cranial nerves usually clears but deafness and blindness usually remain permanent and complete The mortality in early phases of an epidemic has generally been higher than toward the end but this may not be true when chemotherapy is widely used The prognosis in meningococcemia in the absence of meningitis is very favorable The acute cases respond rapidly to either specific antiserum or sulfonamides The outcome in chronic meningococcemia is likewise favorable until the late complications namely meningitis or endocarditis supervene Without any specific therapy the mortality in such cases averaged about 25 per cent Chemotherapy or serum therapy should materially reduce this figure

Treatment —The chief reliance at present is on adequate chemotherapy with sulfonamide drugs which are highly effective both in meningitis and in the meningococcemias in the absence of meningitis

Antimeningococcus serum may be useful as an adjunct While the antiserum may sometimes be employed early in the disease in very severe and rapidly progressing cases its use is usually reserved only for those cases in which proper sulfonamide therapy fails to control the active infection

Chemotherapy—All of the sulfonamide drugs that have come into common use namely, sulfanilamide sulfapyridine sulfathiazole and sulfadiazine are highly effective in the treatment of all types of meningococcal infections Failures from chemotherapy may be expected however when endocarditis is already well established or where attempts are made to clear up the carrier state Sulfadiazine is the drug of choice because (1) it gives the least toxic effects (2) it penetrates well into the cerebrospinal fluid and (3) it is at least as effective as the other compounds There may be situations where it is impossible to supply a sufficient fluid intake in order to insure an adequate output of urine as for example in military units under tropical field conditions Sulfanilamide should then be used because of its greater solubility and the dangers of renal complications will thus be minimized When first introduced sulfathiazole was thought to be contraindicated in the treatment of meningitis because it penetrates poorly into the cerebrospinal fluid where this compound reaches concentrations which are usually about one-third of those found in the blood at the same time Sulfanilamide sulfapyridine and sulfadiazine on the other hand are usually found in the spinal fluid in about 60 to 90 per cent of the corresponding blood concentration In actual practice however sulfathiazole has proved at least as effective as sulfanilamide or sulfapyridine either because of its greater antimeningococcus action or because the concentration of the drugs in the cerebrospinal fluid is not of great importance

Dosage—In general doses of 6 to 9 Gm per day are recommended for adults and 0 03 to 0 1 Gm per kilogram of body weight per day for infants and children the larger doses being reserved for those less than two years of age The dose is the same for each of the four compounds mentioned The initial dose should be equal to a full daily dose and subsequently the daily amounts are given in four or six equal parts evenly spaced throughout the twenty four hours In the case of sulfanilamide or sulfathiazole the four hourly schedule is necessary

Parenteral Administration.—In severe cases in comatose patients or when treatment is begun late in the course of the disease it is advisable to give an initial dose parenterally Sulfanilamide may be given as 0 8 per cent solution in physiologic saline either intravenously or preferably, subcutaneously The other compounds because of their very low solubility must be used in the form of their sodium salts These are administered either as *5 per cent solutions* in distilled water intravenously or as 0.5 to 1 per cent solutions in physiologic saline either intravenously or subcutaneously Intravenous sulfonamides should never be given together with blood transfusions or even in the same apparatus Intrathecal injections have been used either in the form of 0 8 per cent solution of sulfanilamide or as 0.5 to 1 per cent solutions of the sodium salts of the other derivatives in physiologic saline (not in distilled water) While such injections are well tolerated if these concentrations are not exceeded and no untoward effects have been noted from them this procedure is probably unnecessary and is not recommended

Oral treatment should be started as soon as possible but if the patient remains comatose it may be necessary to continue with parenteral therapy for one to three days or even longer In that event the daily dose is divided into three parts and given at eight hour intervals It is desirable, especially in severe cases to maintain blood concentrations of about 10 mg per 100 cc or slightly higher when sulfanilamide or sulfapyridine is used above 5 mg per 100 cc in the case of sulfathiazole and about 15 mg per 100 cc of sulfadiazine

Except when sulfanilamide is used it is important to insure a good urinary output (about 1200 cc daily in adults) throughout the course of treatment and to supply fluids parenterally in the form of physiologic saline or 5 per cent glucose in distilled water if necessary In all sulfonamide treated cases it is also desirable to keep the urine alkaline either by giving sodium bicarbonate orally

with the drugs or by administering sixth-molar sodium lactate solution parenterally if necessary

Sulfonamide therapy should be maintained on full doses until from three to five *days after all evidence indicates that the* infection has subsided that is, after the temperature has stayed normal, the symptoms have cleared, the cerebrospinal fluid has remained sterile and its cellular, sugar, and protein contents have returned to or near the normal values

Antimeningococcus serum was formerly used in every patient in whom meningitis was suspected, and it was administered both intravenously and intrathecally Since the value of sulfonamide drugs has become established very few physicians continue to use antiserum at all except intravenously or intramuscularly in the severest cases The dosage varies, of course with the potency of the preparations and unfortunately, the methods of standardization are not very satisfactory It is also important to ascertain that the serum contains the specific antibodies for the infecting type of meningococcus All the usual precautions for serum injections must be observed The initial injection is usually about 100 cc of unconcentrated preparations or corresponding amounts of concentrated This amount may be repeated at twelve hour intervals if necessary The intrathecal injection of antiserums has been considered responsible for many instances of block in the spinal canal and, since there is no definite evidence that it has any value it is no longer used 'Antitoxic' serum has been recommended by Hoyne in preference to antibacterial serum but it is doubtful whether the former had any therapeutic virtues not found in the latter

Lumbar puncture should be performed for diagnosis before treatment is begun Thereafter the procedure is repeated for relief of the symptoms and signs of increased intracranial pressure for the purpose of obtaining evidence concerning the progress of the infection Care must be taken to allow the fluid to escape slowly drop by drop in order to avoid sudden lowering of the pressure With the use of sulfonamide therapy there is no longer any reason to withhold this procedure from patients suspected of having meningococcemia if there is any sign or symptom of meningitis It is no longer considered good practice to give any medications by the intrathecal route in meningococcal meningitis, and this is true of sulfonamides and of antiserum

The Stage of Sepsis (Meningococcemia without Meningitis) —In this stage the disease readily responds to sulfonamide therapy given in full doses Sulfadiazine at present is the drug of choice

Treatment of Symptomless Carriers—The precise value of antiseptics or vaccines used to eradicate meningococci from the upper air passages is not known It must be recognized that in two thirds of the cases these organisms disappear spontaneously In general it seems better to trust to nature than to impair the integrity of the mucous membranes by strong antiseptics If there is obvious disease of the tonsils, paranasal sinuses, or pharynx this may be eradicated by surgical means, and such measures are often followed by disappearance of meningococci When operations on the upper respiratory tract are undertaken on meningococcus carriers, it is probably wise to administer some sulfonamide for twelve hours prior to the operation and to continue its use for twenty four to forty eight hours later in order to insure against a spread of infection

Cause of Continued Symptoms —Seven days after the beginning of serum treatment *serum sickness* may cause moderate or even high temperature erythema urticaria swelling of the lymph glands enlargement of the spleen or arthritis *Panophthalmitis* may be accompanied by an elevation of temperature so also may *otitis media pericarditis endocarditis meningococcic arthritis hydrocephalus* or other late complications Occasionally *abscess of the cerebrum* may pursue a prolonged febrile and fatal course Serum sickness demands no special treatment Subcutaneous injections of 5 to 10 minims of adrenalin may give transitory relief An eye destroyed by purulent invasion should be enucleated after several weeks have elapsed in order to give a chance for thorough walling off of the focus Pericarditis with effusion should be treated by aspiration and continued chemotherapy Endocarditis is usually evidenced by posi

tive blood culture and is likely to be fatal but active treatment should be tried persistently Arthritis should be treated by rest and if much effusion is present by aspiration Hydrocephalic meningitis or block demands energetic and prompt measures Drainage must be effected within a few days if death is to be prevented Drainage can often be secured by puncture of the *cisterna magna* This should always be resorted to if lumbar puncture does not give a free flow of fluid Puncture of the lateral ventricles is a simple procedure in children and should be carried out without hesitation when there is evidence of obstruction in the subarachnoid space In adults if drainage by the lumbar or cistern route is unsuccessful ventricular drainage can be accomplished by trephining the skull Sometimes a combination of lumbar and cistern puncture or of cistern and ventricular puncture with through and through irrigation with salt solution is effective in securing drainage In the acute swelling of the encephalon in the early stages of the disease which is often shown by bursting headache cyanosis full veins of the forehead and marked delirium the attempt to reduce the volume of the cranial contents by the administration of hypertonic solution of glucose (usually 100 to 200 cc of a 50 per cent solution) intravenously or by the giving of sulfate of magnesium by mouth or rectum is advisable Venesection may also be of use in selected cases Involvement of all the cranial nerves except the eighth usually clears up spontaneously with time Deafness caused by involvement of the eighth nerve in this disease is usually permanent It is possible *though unlikely that relapses may be* guarded against by the use of vaccines during convalescence The administration of three or four doses of 500 000 000 killed meningococci at weekly intervals may be advised

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MENINGOCOCCAL SEPSIS

Not infrequently the meningococcus in its invasion of the blood stream leaves the meninges unscathed Cases of this kind may be acute and not different in clinical aspects from the stage of sepsis already described in the previous section on cerebrospinal fever

However there is a group of subacute or chronic cases of meningococcemia with features meriting separate description In such the picture is that of a prolonged general infection Fever always present is of a very irregular remittent type with quotidian tertian or less frequent peaks often marked by chills The spleen is enlarged and firm The most striking and often diagnostic manifestations are on the skin In addition to the hemorrhagic rashes already described under spotted fever there may be a maculopapular roseola at times mistaken for rose *spots or erroneously called* erythema nodosum or purpura rheumatica These are seen about the joints on the extremities or the torso are generally sparse and appear in successive groups A subacute arthritis may be the chief evidence of meningococcic sepsis Most often the larger joints are involved perhaps successively in a relatively mild type of inflammation with exudate in but not around the joint space

The two most erious results of such a meningococcic sepsis are meningitis and endocarditis Meningitis may occur many months after the onset of the general infection *Endocarditis generally of the mitral*

or aortic valves, runs an acute or subacute course almost always fatal Pericarditis pleurisy, pneumonitis peritonitis and epididymitis are other rarer complications The blood culture is positive A polymorphonuclear leukocytosis is constant

The duration of meningococci infections of this type is most variable They usually last several weeks and certain cases have been prolonged for a year A duration of six months is not rare

The prognosis is by no means discouraging Spontaneous recovery often takes place after months of fever Cases with meningitis have the prognosis of cerebrospinal fever those with endocarditis are almost if not quite hopeless Arthritis clears without residual disability

In the diagnosis one must consider chiefly sepsis of other origin subacute bacterial endocarditis infectious arthritis, rheumatic fever, the purpuras enteric fever the various forms of typhus and erythema nodosum

The treatment consists in the use of the sulfonamides as advised under Chemotherapy in the preceding chapter If necessary this may be supplemented by the intravenous administration of antimeningococcal serum in large amounts—100 cc for an adult—daily for three to five days or until symptoms are controlled It is important to obtain serum from different sources if results are not satisfactory Vaccines may be tried but are experimental Such general measures as transfusion if there is anemia adequate nourishment and supportive measures in general are not to be neglected (See Chemotherapy)

W W HERRICK

BACILLARY INFECTIONS

DIPHTHERIA

Definition—Diphtheria is an acute infectious and contagious disease caused by the *Corynebacterium diphtheriae* or *diphtheria bacillus* It is characterized by the formation of a fibrinous exudate on the mucous membranes of the respiratory tract and by constitutional symptoms due to the absorption of toxins from the local lesion

History—Aretaeus and Galen described ulcerative membranous lesions and Aetius was acquainted with palatal paralysis a frequent sequel to diphtheria Epidemics occurred in the Middle Ages and were described by various English French and Spanish writers Bretonneau gave excellent descriptions of the disease in connection with violent outbreaks in Tours He grouped the diseases known as putrid sore throat, "cynanche maligna and angina suffocativa under the term diphtérite Trousseau who confirmed Bretonneau s observations subsequently changed the name to diphtérie The discovery of the diphtheria bacillus by Klebs in 1883 and its isolation and cultivation one year later by Löffler established the definite bacteriologic entity of the disease In 1888 Roux and Yersin demonstrated the soluble toxin of the disease by passage through a porcelain filter The subsequent fundamental researches of von Behring and Ehrlich dealt with the character of the toxin and the determination of its strength and in 1891 von Behring and Wernicke announced the discovery of antitoxin

Further progress in the control of diphtheria was made when the Health Department of New York City in 1893 adopted under the direction of Park the use of cultures for control of the period of isolation and for diagnosis and when Schick in 1913 described the intradermal toxin reaction for the determination of individual immunity In 1913 von Behring utilized, for the first time injections of toxin antitoxin mixtures in children for active immunization against diphtheria In 1917 Park inaugurated widespread immunization with toxin antitoxin a procedure which has reduced the morbidity and mortality of diphtheria to extremely low levels In 1924 Ramon reported his researches on formalized toxin or anatoxin which later largely replaced toxin antitoxin mixtures for immunization Intubation for relief of obstruction of the larynx was devised by O Dwyer of New York, in 1885 although attempts had been made previously by Bouchut Tracheotomy was especially developed and popularized in the early nineteenth century by Bretonneau and Trousseau whose tube is the standard today

Incidence—Diphtheria occurs chiefly in the temperate zone and is rare in the tropics It is endemic in the larger cities and shows a marked increase in the fall and winter months Outbreaks of great virulence occur at times but since the introduction of active immunization these have tended to disappear

Etiology—Diphtheria is caused by the diphtheria bacillus which is found on the surface of the affected mucous membranes and has very slight capacity to invade the body The symptoms and damages of the disease are due to the toxin which is absorbed from the surface of the infected areas

Contributory causes include *local trauma* as incision or operation on the throat and respiratory infections such as colds measles etc Diseased tonsils favor the malady and tonsillectomized persons are less frequently and less severely affected

Immunity is dependent on the presence in the blood of specific antitoxin which results from recognized attacks of the disease

and is frequently present with advancing age without known attacks having occurred. This "natural" immunity probably results from mild or unrecognized attacks and subclinical infections. At birth immunity is present in about 80 per cent of cases, being derived from the mother through the placenta. This immunity rapidly drops during the first year and at the beginning of the second year only 20 per cent still retain it. It rises definitely from this point to reach about 50 per cent by the tenth year. There is a slower rise through the succeeding age periods, finally reaching about 80 per cent in late life. Immunity is higher for the same age periods in urban than in rural populations, and in crowded sections of cities than among the well-to-do.

Antitoxic immunity as shown by a negative Schick test was believed at first to indicate $\frac{1}{30}$ antitoxic unit per cubic centimeter of blood serum, but numerous subsequent studies have shown that about $\frac{1}{250}$ unit per cubic centimeter more nearly represents the immunity level. There are, however, other factors which influence immunity. In spontaneous recovery antitoxin may not be demonstrable for days or weeks. The influence of wounds in the mouth, throat and skin shows clearly that there is some degree of protection from an intact surface, and it is not improbable that there is also some bactericidal and, possibly, cellular immunity. Immunity after an attack may be short, at least in antitoxin treated cases, and a considerable number lose their immunity in the course of years.

The incidence is highest in children from one to five years of age. In the United States, 64 per cent of all cases occur in children below five years, and over 80 per cent below ten years of age. Since prophylactic immunization was instituted there has been evidence of a rising age incidence, as occurred in smallpox after the introduction of vaccinia. Race influences immunity, and in New York and Boston Schick tests have shown a lower "natural" immunity in Italian children than in other races. Diphtheria is a disease of man; diphtheritic diseases in animals are not due to the same cause. The disease is spread by direct contact or droplets chiefly, and by indirect contact with infected objects such as handkerchiefs, towels, cups, pencils, and toys. The bacillus may remain viable for many weeks if deposited in sputum or membrane. Outbreaks from infected milk were not infrequent before pasteurization. The contamination of the milk occurs directly from human sources or at times, indirectly through infection of the teats.

Bacteriology.—The diphtheria bacillus is a slender rod-shaped organism which in cultures shows marked variation in size, shape and staining. As a rule the bacilli are arranged in parallel or V-shaped formation. They are straight or slightly curved and when stained show granular, barred or solid protoplasm, usually with dark granules at the poles. The granular forms with dark-staining polar bodies are characteristic. The bacillus is gram-positive and can be readily recognized by Löffler's methylene blue stain or by differential stains, such as Albert's, Hunt's or Neisser's. Smears directly from the lesions may show characteristic bacilli in about 80 per cent of the cases but present greater difficulties in recognition than cultures. The bacillus grows well in Löffler's medium of glucose bouillon and blood serum at pH of 7.6.

The organism is readily killed by heat, by tricresol or formalin, and by direct exposure to the sun's rays. It may survive outside the body in pieces of membrane for seventeen weeks.

The diphtheria bacillus produces a *soluble toxin* which is destroyed by heating to 75 C. for ten minutes or to 100 C. for one minute. This toxin when injected into guinea pigs, even in doses as small as 0.02 c.c., causes death in the same manner as when the bacilli have been injected.

Diphtheria-like bacilli comprise a large group, most of which are harmless. Some of these differ sufficiently in size, shape and staining reaction or in cultural characteristics to be separated from the diphtheria bacillus. Others, however, can be distinguished only by virulence tests. The cutaneous test is now more generally used than the lethal test which, however, is somewhat more accurate. *Bacillus xerosis*, which has been found in certain cases of conjunctivitis and on normal and diseased mucous membranes, resembles the barred form of diphtheria bacillus. *Bacillus hofmannii*, the far-

thest removed from the diphtheria bacillus, is a short straight oval bacillus with rounded ends and one lightly stained transverse septum It is nonvirulent

Morbid Anatomy—The lesions of diphtheria are both local and general The former are due to the action of the toxin locally on the tissues at the site of the infection, the latter to the toxin absorbed through the lymph and blood channels

In a series of 251 fatal cases reported by Mallory at the Boston City Hospital a definite membrane which varied in extent and location was observed in 148 patients with the following distribution

Location	No of cases
Larynx	86
Tonsils	74
Trachea	73
Epiglottis	67
Bronchi	44
Nares	43
Soft palate including uvula	15
Esophagus	12
Tongue	9
Stomach	5
Duodenum	1
Vagina	2
Skin of ear	1
Conjunctiva	1

In the living patient the membrane is most frequently seen on the tonsils palate and pharynx

Local Lesions—The local lesions are in all situations essentially of the same character namely, degenerative changes in the epithelial cells and an abundant fibrinous exudation from the blood vessels to the surface and into the underlying tissues As a result there is formed on the epithelial surfaces a membrane which is so striking and characteristic a feature that the disease has been named from it Sometimes when the epithelial cells are necrotic and the destructive process involves the underlying tissue the membrane formation extends into the submucosa The diphtheria bacilli are present on the surface and the superficial parts of the false membrane but in the deeper layers of the false membrane itself they are few or absent

Macroscopically the membrane varies in appearance and consistency The color is usually gray but it may be yellowish green or at times reddish black because of extravasated blood it may be white especially after subsidence begins Usually the membrane retains its form and may be removed or discharged as a more or less complete cast of the structure on which it is formed

Systemic Lesions—The systemic lesions involve chiefly the heart, the kidneys and the nerve fibers The heart muscle undergoes fatty degeneration in more than half of the fatal cases This is always more marked in the vicinity of the endocardium There is also interstitial myocarditis which may lead to extensive formation of fibrous tissue The kidneys show acute degeneration of the epithelium, which leads to cloudy swelling of the cortex Interstitial changes are also fairly common In the more severe cases the kidneys are greatly enlarged The spleen is swollen and congested and the malpighian bodies are prominent Bronchopneumonia is frequently present in infants and young children and is a complication in nearly all the fatal cases of the laryngeal form As a rule it is due to other micro organisms such as the streptococcus or pneumococcus Degenerative changes occur in the peripheral nerves The medullary sheath undergoes fatty degeneration and is broken up into globules The axis cylinder is also involved Both the sensory and motor fibers may be affected but the latter strikingly so There may be degeneration of the columns of the posterior cord Degeneration of the anterior horn cells has also been described

Symptoms—The usual period of incubation is from two to five days The initial symptoms are usually slight and vary greatly with the location of the disease slight fever 99° to 102° F lassitude malaise and sore throat may occur Sometimes the patient does not remain in bed and occasionally marked diphtheria may be found in active children without any complaint The local lesions begin most frequently in the pharynx especially affecting the tonsils the larynx the nose or the nasopharyngeal mucous membrane

Pharyngeal Diphtheria—In the early stages of pharyngeal diphtheria congestion of the fauces and tonsils is followed by the appearance of a thin grayish film which gradually or rapidly thickens until the dense pseudomembrane is present It may be unilateral or bilateral and extend over a part of the uvula palate or postpharyngeal wall

The membrane is raised usually evenly contoured and well defined It is not easily removed until clearing has begun and on forcible removal usually shows small bleeding points Small, spotty multiple patches of membrane are not usual in diphtheria

There may be little or no *edema* but in virulent cases swelling is present and in malignant cases it may be very marked Rarely, swelling may be conspicuous for two to four days before a membrane appears The *redness* in diphtherial inflammation is characteristically dull When intense it often has an almost cyanotic hue As the membrane develops a relatively small margin of the red area is left exposed In advanced cases the absence of redness is often a striking feature There may be *enlargement* of the *glands* or *swelling* of the tissues of the neck which in severe cases may extend from ear to ear and down to or even include the chest In *malignant* cases not treated early the picture is striking The extensive swelling and membrane often becoming dark from hemorrhage the throaty voice and stridor the fetid odor the dysphagia the serosanguineous discharge and the swollen neck are typical The mind is clear but drowsiness and a mild delirium which disappears on waking are often seen Deep stupor or delirium rarely occurs except at the very end

The temperature is usually not high 100° to 102° F though temperatures of 104° F or more are occasionally encountered The temperature may be high at the onset and drop rapidly as the disease advances The pulse varies with the severity of the infection

Hemorrhages from the nose and throat are seen in severe cases and epistaxis is not a rare symptom even in mild cases In the hemorrhagic form hemorrhages from the nose and throat or the genito urinary tract and into the skin and mucous membranes as well as the organs are a striking feature

Nasopharyngeal Diphtheria—Nasopharyngeal diphtheria is of two types the anterior and the posterior In the former the disease is mild and if no extension occurs usually not fatal It is characterized by a serosanguineous discharge which often excoriates the lip and by nasal obstruction The membrane may be seen in the anterior nares on the septum or turbinates or lining the whole nostril It may be obscured by the profuse discharge In mild cases there may be no membrane but many of these can be proved not to be diphtheria even if diphtheria bacilli are present The constitutional symptoms are slight or practically nil and the course in untreated cases is often indolent lasting days or even weeks without much change In the postnasal region on the other hand, diphtheria is frequently malignant and unless promptly treated may have a grave prognosis Swelling high up in the neck below the ears nasal obstruction thick or nasal voice and either nasal or postnasal discharge and obstruction may occur Because of the location the nature of the infection is often obscure The inflammation in a short time may spread downward on the posterior palate or pharyngeal wall into the pharynx In some cases the membrane projects downward from the adenoids like a stalactite

Laryngeal Diphtheria—Laryngeal diphtheria formerly called membranous croup is the most fatal form It occurs most commonly from six months to five years of age but no age is entirely free The onset is characterized by croupy cough followed in a few hours or days by dysphonia or aphonia stridor on both inspiration and expiration and finally dyspnea The accessory muscles of respiration come into use and the respiratory rate may be increased but usually not strikingly so As the obstruction increases the increased respiratory effort may be inadequate and cyanosis appears The patient is restless takes but small amounts of nourishment and shows distress and fatigue If these symptoms continue without relief vasomotor collapse gradually develops the breathing is less forceful cyanosis is replaced by a gray pallor and clammy skin the mental state becomes apathetic and the patient dies The rapidity with which these sequences occur varies with the size and strength of the patient and the virulence of the infection The obstruction may be due to swelling or membrane or both If due to membrane spontaneous loosening and coughing up of the membrane may yield partial or complete relief or if detached and not expelled sudden changes in the degree and character of the obstruction or even complete asphyxia may ensue Large casts of the

larynx or trachea or of the whole pulmonary tree may be brought up

When the membrane extends down the trachea or into the bronchi as frequently occurs this may not be clinically evident until it has been loosened from the tracheal or bronchial wall or until it reaches the bronchioles when dyspnea may occur, usually with increased *expiratory* stridor A valvelike flap in these cases occasionally produces either a marked emphysema or an increased inability to inflate the lungs The dyspnea is alarming and unless promptly relieved is usually fatal Atelectasis and localized emphysema may occur One bronchus may be cut off so that respiration is performed with one lung

Toxic absorption from the larynx and trachea is slight and serious toxic effects such as myocarditis and paralysis seldom occur in infections *limited* to these areas

Diphtheria of Other Parts —Diphtheria of the mouth and tongue is extremely rare and almost invariably preceded by a wound or other infection Diphtheria of the skin is rare but fatal cases have occurred It appears secondary to wounds abrasions or infections such as impetigo varicella or eczema it may rarely occur at the umbilicus in the newborn Diphtheria of the penis after circumcision and of the vulva vagina or cervix during the puerperium has been reported These may be secondary to the nose and throat infection in the same patient or occasionally primary infections brought from an outside source Diphtheria of the conjunctival sac is rare usually complicating the nasal infection Swelling and discharge are marked membrane forms on the conjunctiva and if it extends over the cornea produces permanent opacity Diphtheria of the middle ear may occur as the result of extension from the nasopharynx this is rarely a primary diphtheritic infection but follows infection by other organisms chiefly the streptococcus

Blood —There is a moderate leukocytosis rarely above 15 000 and myelocytes are occasionally present The hemoglobin and red cells usually are decreased during early convalescence The platelets are normal but occasionally may be decreased markedly during the acute stage The blood sugar rises in the early stages of severe diphtheria and the glycogen reserve is lowered There is reduced sugar utilization Later hypoglycemia occurs which gradually disappears as convalescence advances

The blood pressure in the severer cases drops during the first week and reaches its lowest level during the second week after which it gradually rises to normal Cardiac complications cause a sudden drop which may rapidly go below readable levels in fatal cases

Course —Untreated by antitoxin mild cases may rapidly subside even in a day or two but usually the disease increases in intensity up to the seventh or eighth day then if death does not supervene the symptoms gradually subside The nasal cases may persist for two to three weeks With antitoxin improvement begins within thirty six hours and the local lesion subsides in from one to seven days In severe cases secondary shallow ulceration may be seen as the membrane disappears and this may persist for one to two weeks

Complications —*Bronchopneumonia* is the most frequent complication of the laryngeal form especially when the membrane extends down into the trachea and is present in practically all fatal cases In cases of respiratory paralysis usually in the fifth to eighth week bronchopneumonia is very prone to occur *Ulceration* of the throat is not a striking feature of diphtheria It is seen only in the severe forms after clearing of the false membrane Hemorrhage from the nose or throat may be severe and persistent and require packing or other measures *Cervical adenitis* may appear in early convalescence and progress to suppuration *Otitis media* is rare and occurs chiefly in postnasal and extensive faucial cases It may occur secondary to pharyngeal paralysis *Albuminuria* is common in severe cases during the active stage Acute nephritis is rare but may follow in the second or third week and at times is severe

Paralyses occur in about 10 per cent of cases but the rate is much higher in untreated or inadequately treated patients It is a painless peripheral neuritis progressing gradually downward appearing first in the palate at the end of the first or in the second week and last in the legs often after several weeks It gradually increases and then recedes completely disappearing in days to weeks but may persist for three

to four months In the severe cases any or all of the motor nerves may be involved but due to the difference in time of onset and progression involvement is not simultaneous Sensory involvement is less frequent being seen only in the severest cases and occurring later than the motor The smooth muscle fibers are not paralyzed

The distribution of the paralysis is influenced partly by the location of the local lesion In tonsillar or pharyngeal diphtheria the palate shows the earliest and most frequent involvement and if unilateral affects the side of the more marked infection Recurrent *palatal paralysis has been seen* The first paralysis appears early, usually on the fifth to sixth day lasting a week and in unilateral infection is always on the same side The second paralysis appears in the third week and lasts two to three weeks and may be bilateral In cases infected through wounds the paralysis may be localized or appear first in muscles adjacent to the wound

The palatal paralysis produces nasal or cleft palate voice nasal regurgitation and incomplete motion of the palate Paralysis of the constrictors and the geniohyoid group produces dysphagia especially for solids and serious and even fatal choking has occurred from attempting to swallow them There is often great distress choking and gagging from the collection of saliva in the throat There may be marked or even complete anesthesia of the throat

Ocular palsy usually involves the accommodation but strabismus may occur Paralysis of the face neck trunk arm or leg may occur usually progressively but the legs are usually more strikingly affected The knee jerks are diminished or lost although at first they may be increased There is a varying degree of reaction of degeneration

Even in the most extensive cases it is rare to find any muscle except the palate in which some observable motion cannot be made out

In the late stages there may be marked ataxia especially of the legs associated with the loss of sense of position In sensory paralysis the acuity of pain sense may be diminished more than tactile sense although both are not often completely lost Perception of heat and cold is not affected Other disturbances of the sensory mechanism such as paresthesias and formication may be found

Respiratory paralysis due to phrenic damage is the only paralysis that may prove fatal and it usually occurs in the fourth to eighth week of illness

Paralysis of the larynx appears usually in the third week and causes dysphonia or aphonia Wolcott found laryngeal obstruction due to abductor paralysis in 48 of 478 cases of paralysis In laryngeal diphtheria it is difficult to distinguish toxic paralysis from local injury

Cerebral paralysis may follow diphtheria producing monoplegia or hemiplegia In our eight cases it has always been due to a thrombosis of a cerebral artery and has manifested itself as a partial or complete hemiplegia It may completely or partially disappear and is probably the only type of permanent paralysis due to diphtheria It may occur with diphtheritic paralysis concomitantly

Cardiac Complications—In about 5 per cent of patients chiefly in the severe toxic cases heart disease occurs in some form The onset is from the sixth to the twenty first day the symptoms being sudden pallor and listlessness often associated with nausea vomiting and pain in the epigastrium The blood pressure drops The epigastric pain may be marked and suggestive of an acute abdominal condition The liver is often enlarged and usually tender The area of cardiac dulness may be increased and the cardiac impulse soft and diffuse However in many cases no dilatation can be made out Vomiting may be severe and persistent but usually ceases on stopping food and fluids The pulse rate may drop remain unchanged or become rapid The first sound is softened and frequently the diastolic pause is shortened Arrhythmia is the most common finding and every type of abnormal rhythm may occur There are often rapid changes in the type of arrhythmia Electrocardiograms show in the main two types of injury (1) T wave changes (2) auriculoventricular and intraventricular block In the first recovery usually occurs while in the second except in the mild form death ensues Most deaths occur within three days after the onset it is rare to have patients die after

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as occurring in lymphatic and myelogenous leukemia and in aplastic and pernicious anemia as well as in syphilis

LARYNGEAL DIPHTHERIA—Croup should always be considered and treated at once as diphtheria unless the latter can be definitely excluded When associated lesions occur in the throat or nose the diagnosis of diphtheria may be made easily but when primary in the larynx recognition may be difficult without laryngeal examination When the infection in the larynx is diphtherial a characteristic membrane may not appear at once and in some cases streptococcic infections may have an exudate closely simulating diphtheria In diphtheria the signs usually show gradual progressive development but in exceptional cases progress may be very rapid

SPASMODIC CROUP is characterized by a sudden onset of croupy cough and stridor frequently at night and by frequent remissions often complete during the day Dyspnea may be variable Dysphonia and aphonia are usually absent but this is also true in diphtheria below the vocal cords The history of previous attacks is valuable Laryngeal examination shows only redness and adduction of the cords due to spasm

LARYNGISMUS STRIDULUS occurs in tetany usually associated with marked rickets The stridor is purely *inspiratory* and there is no dyspnea

LARYNGOSPASM producing stridor and croupy cough may occur in a variety of neurologic states such as poliomyelitis with bulbar involvement and basilar meningitis

EDEMA OF THE GLOTTIS due to inflammation of the epiglottis and aryepiglottic folds produces an *inspiratory* dyspnea without dysphonia and is often associated with high fever and great prostration It can be easily diagnosed by palpation or laryngoscopy Diphtheria produces supraglottic edema only when there is severe faucial involvement

RETROPHARYNGEAL ABSCESS causes only *inspiratory* stridor until the abscess is very large There is dysphagia and no dysphonia There may be cervical adenitis which is not found in laryngeal diphtheria Palpation of the postpharyngeal wall discloses the swelling

FOREIGN BODY—The sudden choking attacks which usually occur in lodgment of a foreign body may not be observed in young children and instead gradually increasing signs of obstruction may occur Laryngoscopy is important Routine laryngoscopy in cases of supposed diphtheria has repeatedly shown foreign bodies Obstructions below the suprasternal notch produce *expiratory* stridor and there is no croupy cough nor dysphonia The expiration is usually long and wheezing

THYMIC ASTHMA is rare Laryngoscopy shows a normal larynx

ACUTE LARYNGITIS due to streptococcal influenzal or other bacterial infections cannot be distinguished certainly without laryngoscopy and laryngeal cultures It is safer to give antitoxin unless it is known that the patient has a negative Schick reaction

Bacteriologic Diagnosis—Cultural diagnosis naturally has been of the utmost value in this disease Atypical cases both very severe and very mild as well as carriers would be frequently missed without it It must be noted that the presence of diphtheria bacilli in cultures from a lesion does not necessarily prove diphtheria to be present This may be readily demonstrated in diseases such as syphilis where the lesion may be accurately identified In cases such as mild tonsillitis when diphtheria bacilli are obtained demonstration of adequate antitoxic immunity is necessary In any case clinical safety suggests the accepting of diphtheria bacilli in cultures as indicating the disease until otherwise proved

When bacilli have been shown to be non virulent diphtheria may be dismissed More rapid growth for diagnosis has been secured by Brahdy by preparing the swabs with media incorporated into the cotton By this method good smears may be secured in four hours In rare instances patients with negative Schick tests exposed to diphtheria develop membranous lesions typical of mild diphtheria and show virulent diphtheria bacilli These cases are mild get well rapidly without treatment and do not develop toxic effects

CULTURAL TECHNIC—For accurate results the following details should be followed the swab should be applied only to the area of inflammation and *thoroughly* rubbed over it If there is a thick membrane it is better to

the third week of *diphtheria from* this cause Complete ultimate recovery is the rule in the nonfatal cases although a few cases may show electrocardiographic changes and varying degrees of circulatory failure for long periods Clinical evidence of marked fibrous myocarditis is rarely found although histopathologic studies would suggest it as a frequent sequel

Diagnosis —Early *diagnosis is of* the utmost importance but antitoxin should be used at once in all cases where the findings suggest diphtheria and its certain exclusion is impossible After *some experience* it is possible to decide in which cases it is *safe* to wait for cultural evidence Any swelling or membrane in the throat, croupy cough *dyspnea or postnasal* infection is sufficient reason for antitoxin treatment unless the *physician can identify* the lesion as unquestionably not diphtheria The *most significant* features are the translucent gray membrane which later becomes dense sharply defined and evenly contoured the relatively slight redness surrounding the membrane and the peculiar rather soft swelling of the throat and neck in the severer cases In the nasal cases the seromucoid, often blood tinged associated discharge with nasal obstruction is characteristic while in the laryngeal cases croupy cough dysphonia, and stridor are typical The fever is usually slight or moderate and general toxic symptoms are mild, except in advanced cases

Differential Diagnosis —Follicular or Lacunar Tonsillitis —The membrane is in multiple specks or larger masses often closely placed the redness is usually brighter, more extensive and the constitutional symptoms more marked than in diphtheria Evidence of immunity by a negative Schick test is of value A diphtheritic membrane however may start as small tonsillar specks and some observers consider this the usual picture in mild cases

Peritonsillitis —In peritonsillitis there is a bright extensive redness a firmer more tender swelling the swelling is more apt to be confined to the glands which are hard and tender and there is more dysphagia pain and difficulty in opening the mouth When fluctuation can be made out by the exploring finger the diagnosis is assured

Septic Throat and Scarlet Fever —The membrane in these conditions is apt to be whiter, with more irregular margins, and often *more friable*, ulceration is frequent and the most important characteristic finding *is a brighter*, more extensive redness beyond *the membrane* The toxic symptoms are usually severe and high fever, vomiting and delirium may be present In scarlet fever the eruption and strawberry tongue in addition to the characteristic throat and rash, usually distinguish it from diphtheria

Vincent's angina occurs invariably as a sharply defined ulceromembrane The membrane is friable has a foul odor and when *removed leaves a* dirty base Surrounding inflammation is slight or absent Swelling and glandular reaction are absent or slight and constitutional symptoms mild In addition to the faucial lesion there is usually an ulceromembranous gingivitis which may be limited to a small area, or involve the whole gingival margin The smear shows predominating *Bacillus fusiformis* and *spirochetes of Vincent*

Agranulocytosis —Membranous ulceromembranous or phlegmonous lesions of the throat may occur with neutropenia They are more notable for their variety than for distinguishing features Prostration out of proportion to the lesion persistence of the lesion and inconsistencies in the clinical appearance may suggest a blood examination which will make the diagnosis A routine white blood count is desirable in throat lesions In *monocytic angina* membranes and ulceromembranes are often distinguished with difficulty from diphtheria The slow course often a prodromal illness of a few days preceding the sore throat and the differences in the lesion may be helpful in differentiation The increased monocytes in the blood and the heterophile agglutination in the blood are important aids In many cases general glandular enlargement and splenomegaly will indicate the disease

Thrush —The white curdled milk like membrane of thrush may occur in large patches sometimes producing extensive membranes over tonsils pillars uvula and palate The surface is usually granular or matted and friable and pieces of the exudate show mycelial threads or spores

Lesions of the mucous membranes at times simulating diphtheria must be kept in mind

in many cases Rare instances occur where it is lost within one to two years The fact that the toxoid has been given should not be accepted as evidence of immunity until a subsequent Schick test is negative Reactions to the toxoid are infrequent, local and mild although slight malaise and fever on the following day may occur especially in older children Immunity develops slowly in from one to four months but may appear even after a year Nearly the same results are obtained with toxin antitoxin mixtures containing 0 1 lethal dose of toxin In older children and adults the reactions are somewhat less than with toxoid There is some sensitization to horse serum unless goat or sheep toxin antitoxin is used Alum precipitated toxoid because of its slow absorption and absence of rapid elimination may be given in a single dose Better results are obtained with two injections but at present the soluble toxoid in three doses produces optimal results Differences in absorption make alum precipitated toxoid slightly less certain than soluble toxoid

The *Schick test* is done by intracutaneous injection of 0 1 cc toxin solution containing $\frac{1}{50}$ M L D A special syringe and a 26-gauge short bevel needle are desirable The injection should produce a distinct wheal A control test is done in the same manner with a similar solution heated to destroy the toxin

The reaction to the toxin appears in twenty four to forty-eight hours increases for four to five days and varies in size from 1 to 7 cm in diameter Severe reactions may be vesiculated Subsidence begins in about a week and pigmentation followed by desquamation often results The area may be distinguished for months in some cases Reactions in the control tests result from foreign protein contained in the medium or in the bacillus and show no relation to immunity They appear in eighten to twenty four hours and usually subside in two to three days

A reaction to the toxin shows lack of immunity When the control test is negative positive and negative Schick tests are easily determined by the presence or absence of reaction When there is reaction at the control area a positive Schick test (combined reaction) *is determined by (1) the larger* size (2) the longer period to reach the height of the reaction (four to five days) and (3) the later pigmentation and desquamation If the Schick and control tests are exactly parallel the test is negative (pseudoreaction) and the patient immune Exposed children who have not been subjected to the Schick test may be protected by subcutaneous injections of 1500 to 2000 units of antitoxin This passive immunity lasts for two to three weeks This procedure may be omitted if careful daily examinations and cultures from the throat and nose are taken If the cultures are positive or if symptoms appear antitoxin should be given at once

The prevention of the spread of diphtheria requires the following procedures

1 All patients, as well as carriers should be promptly isolated

2 Isolation should prevent direct or indirect contact of the patient with others by sterilization of (1) dishes (2) linen and (3) other utensils when taken from the isolation zone and by protection of the clothes face etc., of attendants by gowns with the usual aseptic technic Sterilization should be done by boiling dry heat baking chemical disinfection with 1 per cent trikresol solution or other disinfectants or by exposure to direct sunlight for a few hours

3 The patient must be kept under these precautions until shown free of diphtheria bacilli by two or more consecutive daily negative cultures

4 Terminal disinfection while of little importance should be carried out as indicated especially on objects in intimate contact with the patient s nose and throat or with his secretions Aseptic technic in the care of the patient and concomitant disinfection during the acute and convalescent stages renders the patient s surroundings comparatively free from infection by the time the bacilli have disappeared from the mucous membranes

Treatment — *General* — The patient should be kept in bed and as free from exertion as possible not only during the acute stage but until danger of cardiac injury has subsided (at least three to four weeks) Allowing activity before this such as getting out of bed should be countenanced only *when the physician is certain that the tox*

swab the edge In laryngeal infection, if primary, the swab should be taken directly from the larynx, preferably through a laryngoscope For carriers, all the parts of the upper mucous membranes must be swabbed The swab should be well rubbed over the Loffler slant

Reliable results can be obtained only after six to eight hours incubation at 37° C and preferably after eighteen to twenty hours Negative reports should not be accepted as excluding diphtheria, even if the above details are completely followed unless repeated two to three times Positive reports do not prove that diphtheria is present but should always be so accepted until diphtheria is excluded

Prognosis —The chief factor in prognosis is the prompt administration of an adequate amount of antitoxin A few hours delay in the administration of antitoxin in a rapidly developing case may make a grave difference in the prognosis Table 1 taken from Ker is representative of a series of cases which various authors have reported

TABLE 1

RELATION OF MORTALITY IN DIPHTHERIA TO TIME OF ADMINISTRATION OF ANTITOXIN (Ker)

Day	*Patients*	*Deaths*	*Fatality rate*
First	329	5	1.5
Second	2269	77	3.3
Third	2407	165	6 8
Fourth	1612	176	10.9
Fifth	911	136	14 9

Age is an important factor The younger the patient, the higher the mortality rate the latter being especially high during the first two years of life

The location of the infection has an important influence Laryngeal infection before the use of antitoxin had a fatality rate of about 90 per cent The deaths are chiefly due to asphyxia and bronchopneumonia Faucial and nasopharyngeal diphtheria are associated with rapid absorption of toxin while infection of the anterior nares skin and other locations is rarely followed by severe toxic damage Swelling of the throat and neck rapid formation of membrane and hemorrhages denote grave danger Deaths during the first week occur usually from acute toxemia or from complicating infections During the second and third week deaths are from myocarditis or secondary infection, and later, especially about the fifth to eighth week from respiratory paralysis

Mortality —Before the discovery of antitoxin the fatality rate in diphtheria was about 35 per cent and in laryngeal cases about 90 per cent but since its discovery the mortality is approximately 5 per cent and in the laryngeal cases 15 per cent These figures are influenced by early treatment and in the laryngeal form by many factors in management The community death rate has dropped steadily for a long period and since active immunization, has reached a low level Table 2 gives the mortality for Massachusetts in five year periods

TABLE 2

DEATH RATE PER 100 000 POPULATION IN MASSACHUSETTS

1870–1874	49 9	1905–1909	22 1
1875–1879	154 6	1910–1914	17 1
1880–1884	106 9	1915–1919	18 0
1885–1889	84 8	1920–1924	14 6
1890–1894	64 0	1925–1929	6 5
1895–1899	51.2	1930–1934	2 6
1900–1904	35 4	1935–1938	0 5

Prophylaxis —Control is practicable only by active immunization It is not essential to procure immunity in 100 per cent of the population as experience has shown that if 85 per cent are immune they will prevent an epidemic the non immunes being protected by the immunes

Immunity is secured by administering toxoid or toxin antitoxin mixtures to all children in early life preferably between six months and one year of age Toxoid or anatoxin is rapidly displacing the toxin antitoxin It does not sensitize to foreign serum but produces slightly more reactions in adults and older children The toxoid is given in three doses of 0.5 1, 1 cc subcutaneously at intervals of three to four weeks A Schick test should be done in six months and if immunity has not developed another series of toxoid injections should be given While the highest value of active immunization is secured by applying it in the latter part of the first year, it may be used with valuable effect later in the school age and in adults who are brought especially into contact with this disease Immunity so secured lasts for many years and probably for life

in many cases Rare instances occur where it is lost within one to two years The fact that the toxoid has been given should not be accepted as evidence of immunity until a subsequent Schick test is negative Reactions to the toxoid are infrequent local and mild although slight malaise and fever on the following day may occur especially in older children Immunity develops slowly in from one to four months but may appear even after a year Nearly the same results are obtained with toxin antitoxin mixtures containing 0 1 lethal dose of toxin In older children and adults the reactions are somewhat less than with toxoid There is some sensitization to horse serum unless goat or sheep toxin antitoxin is used Alum precipitated toxoid because of its slow absorption and absence of rapid elimination may be given in a single dose Better results are obtained with two injections but at present the soluble toxoid in three doses produces optimal results Differences in absorption make alum precipitated toxoid slightly less certain than soluble toxoid

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Treatment — *General* — The patient should be kept in bed and as free from exertion as possible not only during the acute stage but until danger of cardiac injury has subsided (at least three to four weeks) Allowing activity before this such as getting out of bed should be countenanced only when the physician is certain that the tox

emia has been comparatively mild This is not easily determined The diet should be liquid and should contain adequate carbohydrates sufficient vitamins, especially B and C and a minimum of proteins During the acute stage a liquid diet is preferable

Acute Myocarditis—The most important factor is *complete rest, constant horizontal* position with the head low, and avoidance of all unnecessary handling and activity Nausea and vomiting frequently require starvation for a period and 50 per cent glucose solution intravenously, usually 25 to 50 cc should be given two to four times daily One unit of insulin for each 2 5 Gm of glucose should be given subcutaneously It may be necessary to continue this medication for more than a few days Morphine subcutaneously, should be given to secure rest and quiet as needed Cardiac stimulants have little value Digitalis may rarely be of aid but it may do harm by increasing the heart block Caffeine sodiobenzoate is of value in vasomotor collapse

Paralysis—Usually no treatment is required There are no postural problems due to contractures and recovery is the invariable rule Permanent paralyses are due to other causes such as thrombosis and are rare Respiratory paralysis is best treated in a respirator and if marked such recourse is essential Changing the posture to avoid hypostatic pneumonia is important If there is inability to swallow it is helpful to turn the patient on the face to avoid the constant choking from saliva If paralysis of the swallowing muscles is associated with respiratory paralysis suction can be used to minimize the discomfort Atropine may be used to reduce salivation Feeding must be done with a stomach or duodenal tube through the nose or the mouth

Antitoxin Treatment—The greatest advance in the treatment of diphtheria has been the discovery of antitoxin and its effectiveness depends on administration of an adequate amount early in the disease Patients treated on the first day of infection practically always recover but the mortality rises with each day s delay

The clinician should administer at once adequate antitoxin to every case of inflammation of mucous membranes in a child unless he can determine with sufficient certainty either that the condition is *not diphtheria* or that delay for a complete diagnosis will not endanger the patient Antitoxin has no effect on the cardiac damage or paralysis after they have appeared The total dosage should be given at once In severe cases the intravenous route is advisable while in milder cases intramuscular injection is satisfactory preferably into the upper gluteal region The dose must be adjusted to the amount of toxemia, which is best indicated by the severity of the local inflammation and the rapidity of advancement Park varies the dosage with the weight of the patient from 150 to 600 units per pound of weight in mild cases to 1000 to 6000 per pound in the severe ones In Denmark and at the South Department, Boston City Hospital very large doses are favored For mild cases 5000 units are given for moderate cases 10 000 to 20 000 units for severe cases 30 000 to 50 000 units and in malignant cases as high as 100 000 units or more

The effect on the local process will be observed within twenty four to thirty six hours Friedemann has seen the first improvement as late as the third day The swelling begins to subside, the membrane bleaches and loosens at the edge or shrinks the discharge ceases and the temperature drops The patient often feels better before the local improvement is seen Even after enough antitoxin has been given the swelling and membrane may spread rapidly for twenty four to thirty hours or if the membrane is removed it may re form due to toxin already fixed in the tissues and not influenced by antitoxin

Serum Sickness and Shock—*Reactions* to horse serum may follow the administration of antitoxin They occur in about 15 per cent of cases This reaction is influenced by the dosage small doses producing few reactions while a dosage of 100 cc will excite a reaction in about 90 per cent of cases For reasons not entirely clear antidiphtherial globulins are less likely to cause reactions than antiscarlatinal globulins

Sudden *shock* with substernal oppression dyspnea cyanosis angioneurotic edema and extensive urticaria may occur in persons sensitive to horse serum Rarely there is a fatality the incidence being about 1 in

25 000 to 35 000 cases The danger can be in large part predetermined by tests although it is possible that these may be misleading Sensitization tests should be performed by either the intracutaneous or conjunctival method The conjunctival test seems slightly less sensitive than the intradermal although this is not universally agreed and consequently a positive test is more conclusive

The Intracutaneous Test —A solution of horse serum or the serum to be used is injected *intracutaneously* in a dose of 0 01 to 0 001 cc Positive reactions appear usually within two to five minutes and occasionally within fifteen minutes manifested by redness and a spreading wheal 1 to 2 cm or more in diameter with pseudopod formation A history of allergy in the patient is important even though he may not be sensitive to horse serum

The conjunctival test is done by dropping one drop of serum (1 to 10 dilution) into the sac Positive reactions appear within five minutes with itching redness and swelling of the conjunctiva and lids If marked the reaction can be abated by a drop or two of 1 1000 solution of adrenalin dropped into the eye

All patients showing positive reactions do not react unfavorably to serum However fatal results from serum in cases with mild skin reactions have been reported

If serum must be used in a patient showing a positive allergic reaction and if there is no antitoxic serum of a type to which he is not susceptible desensitization should be done by giving subcutaneously gradually increasing doses at fifteen to thirty minute intervals starting with the test dose Each subsequent dose may be doubled but if a reaction appears the next dose and subsequent doses should not be increased until no ill effect results from its use

Adrenalin should be ready to administer if symptoms are severe Adrenalin is often given with the serum or five minutes preceding its administration and is of definite value in protecting against reactions

It may be impossible to desensitize some patients and some observers believe that it is impossible to rapidly desensitize ' atopic cases They contend that hypersensitivenes acquired by previous contact with the serum does not produce fatal anaphylactic shock and that fatal shock occurs only in case of spontaneous hypersensitiveness (atopy)

Serum sickness appears after an incubation period usually of six to twelve days occasionally up to twenty-one days It may appear in sensitized persons in a few minutes or during the first day Urticaria is the commonest symptom and may be local at the site of injection or general Multiform erythema is less common and usually appears in a week It may be morbilliform circinate or rarely scarlatiniform Angioneurotic edema especially of the face and hands may occur usually associated with urticaria Adrenalin in doses of 10 to 15 minims given subcutaneously relieves urticaria for one to two hours and may be repeated as needed It may produce sudden nervousness tremor tachycardia and even eye symptoms in hypersensitive patients Local sedatives such as calamine lotion menthol alcohol solutions and soda bicarbonate may be used and general sedatives such as phenobarbital may give relief The patient should be kept cool and quiet

Arthralgia usually without signs of active inflammation is a distressing serum reaction It is apt to be multiple lasting three to four days or rarely longer and pain is chiefly due to motion Immobilization gives relief

The Arthus reaction may occasionally appear at the site of injection of serum within twenty four hours as a reddened tender swollen area simulating an infectious cellulitis It reaches its height in two to three days and usually subsides in a week Local necrosis may occur in severe cases It is apt to appear in patients who have previously had serum We have seen over 25 per cent of a large group of boys develop this reaction on a second injection of serum one week after the first

Local Treatment —Local treatment has no effect upon the toxic damage and may be actually harmful Throat irrigations with warm salt solution or 25 per cent glucose solution may be used if they do not tire the patient Nasal irrigation is likely to increase the incidence of otitic infection Suction with a small catheter will often give marked relief

Laryngeal Diphtheria —In addition to the prompt administration of antitoxin this form frequently requires mechanical relief of ob

struction due either to membrane or swelling but usually to both Spasm usually plays no part and a steam tent may increase the dyspnea more than cold outdoor air Exertion, such as crying walking and talking increases the dyspnea since the need of oxygen cannot be entirely met and the greater respiratory effort further increases the oxygen demand

When obstruction is due to the membrane relief may be obtained by suction through the laryngoscope with special tubes or by swabbing or, less rapidly by forceps The membrane is readily detached from the *trachea and slightly less so from the larynx* It may re form in six to twelve hours and require removal and this may recur up to twenty four or thirty six hours *after* antitoxin has been given If swelling is the main cause of obstruction an intubation tube may be inserted with complete relief The degree of stenosis requiring this is difficult to define It should not be postponed until fatigue or cyanosis appears Increasing obstruction leads to physical exhaustion partial anoxemia acidosis fluid and food starvation hypoglycemia and the accumulation of mucopurulent material below the stricture and these factors strikingly predispose to pneumonia When a child at rest shows stridor and use of the accessory muscles of *respiration intubation should be done* Sedatives if used must be given with great care A patient exhausted before intubation often goes to sleep at once thereafter and should not be fed by mouth or disturbed until he has had a breathing spell and regained active reflexes

Low obstruction may occur in the trachea or bronchi from partial detachment of a membrane or by attempts to expel a cast from below This may appear suddenly with complete obstruction requiring immediate treatment or it may produce a gradually increasing dyspnea which is distinguished from pneumonia or toxic dyspnea by the characteristic stridor These low obstructions are best relieved by suction through the laryngoscope or bronchoscope

The intubation tube is removed in four to seven days If swelling persists reinsertion may be needed using a smaller size If antitoxin has been properly given continued stenosis is due to *secondary infection* or trauma and if persistent for two to three weeks may indicate tracheotomy

Feeding should be with liquids and semisolids and patients often swallow better in the sitting position Nasal feedings are usually unnecessary Fluids such as glucose and salt solution may be given intravenously or by hypodermoclyses

TRACHEOTOMY—Tracheotomy for relief of diphtherial obstruction has been largely replaced in the United States by intubation It must be used however, when the obstruction is above the larynx as in severe faucial diphtheria In some cases of extension of the *membrane far down the bronchial tree* it has an advantage in allowing easier instrumentation with bronchoscopes but usually the long suction tubes make this unnecessary *In cases where laryngeal tubes or in*struments are not available tracheotomy may be imperative The indications are the same as for intubation and Trousseau emphasized the harm of waiting until the last moment before resorting to the operation

Tracheotomy patients require constant supervision and the inner tube must be removed and cleaned frequently It must be boiled before reinsertion If obstruction occurs below the tube the whole tube may be removed the wound held open by spreaders and the obstruction removed by *suction swabbing or forceps* Relief may be obtained by suction with a catheter passed through the tube Lubrication of the trachea with sterile vegetable oil such as oil of sweet almonds may assist in coughing out secretions The tube is kept until the stenosis subsides a point which can be ascertained only by removing the tube from time to time

Chronic Stenosis of Larynx—Persistent stenosis results usually from secondary infection chiefly streptococcal which invades the laryngeal tissue and causes ulceration chondritis or perichondritis and sometimes peritracheal abscess or it may follow pressure necrosis from too large tubes or trauma in inserting or removing the tube Some observers ascribe it to paralysis It is much more common in infections other than diphtheria Tenderness of the laryngeal cartilages is found on palpation when there is chondritis This symptom is not present in simple diphtheria of the larynx If any of the causa

tive factors above mentioned is discovered tracheotomy, usually low, should be done or if stenosis persists even without obvious cause for two or three weeks tracheotomy is to be seriously considered After tracheotomy, the larynx should be left alone until healing is completed when dilatation or other operative treatment may be undertaken

Carriers.—The treatment of carriers is unsatisfactory and no specific is available If there is a definite focus of infection in the tonsils tonsillectomy will usually be followed by disappearance of the diphtheria bacilli from the throat Before tonsillectomy, cultures should be taken from all the various areas for several days to determine the point or points of infection These are frequently limited and if confined to the tonsils recovery after tonsillectomy may be confidently predicted Outdoor living and exposure to the sun are of great value and the carrier state is less frequent in the summer Sinus infection is a frequent cause of the carrier state and should be treated if present Subacute pharyngitis can often be treated successfully with a 5 per cent silver nitrate solution

A great variety of antiseptics are used such as gentian violet 2 per cent mercurochrome and various acids applied by swabbing or sprays The frequent failure of these is probably due to the difficulty of reaching the organisms in the throat or nose Persistent use of germicides or simply persistent waiting may be followed by success

Treatment of the carrier is not indicated if the organisms are nonvirulent and this should be determined at the outset A great majority of clinical cases rid themselves of the bacilli within two weeks after recovery from diphtheria and the contact of these cases with other diphtheria patients even for long periods rarely induces the carrier state

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TETANUS

(*Lockjaw*)

Definition.—Tetanus or lockjaw is an infectious disease in which the symptoms are due to the toxin produced by the causative organism *Clostridium tetani*

History —The manifestations of tetanus are so *dramatic that it has been recognized as a* clinical entity for centuries In fact, both the systemic and the regional forms of the disease are clearly described in the writings of Hippocrates The transmissibility of tetanus was shown in 1880 and the actual causative agent was identified by Nicolaier in 1884 An immense amount of study was devoted to this malady during the twenty years following the isolation of the *Clostridium tetani* This work culminated in the experiments of Meyer and Ransom which seemingly proved that the clinical manifestations of tetanus were due to the passage of the tetanus toxin up the motor neurons of the central nervous system This theory was universally accepted until the last decade when it was challenged and probably refuted by Abel and his coworkers who claimed that the toxin reached the central nervous system by the blood stream The other great milestones in the mastery of this frequently fatal infection were the development of specific antitoxin (Behring and Kitasato) and the production of toxoid for active immunization

Incidence —Virtually all warm blooded animals are susceptible to tetanus The disease is found wherever the soil is contam

inated by animal or human excreta Recent inquiry into the occurrence of tetanus spores on the pavements of Baltimore show an incidence of 17 per cent The number of deaths reported in the United States in 1936 were 1088 but doubtless there were many unreported cases Regions of the country in which the soil has been intensively fertilized have a distinctly higher incidence of tetanus than less cultivated areas During the early months of the first World War the occurrence of the disease among the British Expeditionary Forces was exceptionally high (32 per 1000 wounded) The mandatory administration of tetanus antitoxin to all wounded soldiers corrected this condition so that when the American troops became active in France, only 36 among the 224 089 wounded developed tetanus (0 16 per 1000)

Etiology—The etiologic agent is always the same but the manner in which the spores or the organisms enter the body is not always apparent There are numerous ways in which this may occur Frequently an insignificant wound suffices to admit the organism Sometimes it is impossible to find the point of entrance or the locus of infection Contamination of the umbilicus of the new born is still an all too frequent occurrence The planting of spores into clean operative wounds during dust storms has become a real source of infection in certain parts of the United States Compound fractures the wounds from blank cartridges embedded splinters and puncture wounds of the feet are frequently the forerunners of tetanus Bee stings insect bites burns hypodermic injections and bed sores contaminated with fecal matter have been known to be sources of this infection The mere deposition of spores into the tissues does not suffice to produce clinical manifestations of tetanus There must be concomitant necrosis of tissue due to trauma or a foreign body or an associated pyogenic infection to facilitate the growth of the *Clostridium tetani* The spores germinate only where there is diminished oxygen tension

Bacteriology—*Clostridium tetani* is a slender slightly motile rod from 2 to 5 microns in length Various strains differ in their pathogenicity They tend to grow singly and the development of a spherical spore gives the sporulative form a characteristic squash racket appearance *Clostridium tetani* perpetuates itself outside the animal body and spores are found in earth, manure and putrefying liquids They are found in the intestines of many ruminants horses and herbivora as well as in the stools of humans Bauer and Meyer found that approximately one in every four specimens of human feces contains tetanus spores The spores are unusually resistant to the methods commonly used to kill bacteria Mercurial preparations cannot be relied upon for this purpose formaldehyde is the most effective of the commonly used antiseptics When sterilization by heat is used one cannot rely upon boiling to destroy the spores but must autoclave the material to be sterilized at fifteen pounds pressure for twenty minutes (121° C)

The toxin produced by *Clostridium tetani* is probably the most potent water soluble poison known to man The strength of the toxin varies according to the strain of the organism used and also according to the culture medium One of the most potent toxins ever obtained has been prepared by Brewer using a modified Maclean technic This toxin was so strong that $1/_{000\,000}$ of a cc killed a 20 gram mouse in two hours The most interesting factor concerning this particular toxin is that the toxoid made from it evokes a very high immunity without producing any demonstrable antitoxin in the blood of guinea pigs

Bacteriologic Examination for Clostridium tetani Although *Clostridium tetani* is one of the easiest organisms to identify the actual isolation from surgical material presents some difficulties due to the small number of organisms usually present in wounds and the fact that the foci of infection are often small or even insignificant Debrided material should be obtained from the depth of the wound and placed into thioglycolate and cooked meat medium Duplicate cultures should be made and one set heated to 80° C for twenty minutes to kill off all organisms except the spores Then both sets of tubes should be incubated forty eight to seventy two hours and examined for gram positive bacilli with round terminal spores *Clostridium tetani* sporulates better in cooked meat medium if only a few organisms are present however growth will be initiated more read

ily in the thioglycolate medium Blood agar plates or thioglycolate agar plates should be made at this time and isolated colonies may be picked to insure pure cultures

Pathogenesis —Until the last decade there were two cardinal theories concerning tetanus that were widely accepted The first was the unitary theory which held that the disease was solely one of the central nervous system The second was the nerve carriage theory, propounded by Meyer which maintained that tetanus toxin unlike all other water soluble toxins reached the central nervous system through the peripheral nerves Abel questioned the correctness of both of these theories and drew attention to the fact that the theory of neutral transport of tetanus toxin rested on several unproved assumptions In addition to his logistic objections Abel demonstrated the production of local tetanus in experimental animals by the intramuscular deposition of minute quantities of tetanus toxin at multiple points As little as $\frac{1}{8000}$ of the usual lethal dose of toxin if placed in each of forty different places in the muscles of a hind limb of an animal renders that limb rigid for several weeks This fact however is indirect evidence of the local action of tetanus toxin subsequently Harvey showed by oscillographic studies that the site of action in local tetanus is at the neuromuscular end organ

At the same time a successful effort was made by Abel s associates to produce separately the other cardinal manifestation of tetanus namely clonic convulsions To do this minute quantities of tetanus toxin were put into an anterior horn of the dog s spinal cord It was found that following the injection there is a latent period free from any detectable changes The deep reflexes then become hyperactive to the slightest sensory stimulus It is possible to produce clonic movements in such a limb by gently blowing one s breath upon it No evidences of unyielding rigidity (local tetanus) are observed in this experimentally produced central form of the disease It was during the performance of these experiments that a wholly unexpected discovery was made namely that all of the animals died despite the fact that the amount of toxin injected into the lumbar cord was only a fraction of the ordinary intravenous lethal dose It was found that the intraspinal injection of as little as $\frac{1}{400}$ of the usual lethal dose is always followed by the death of the animal even though the toxin is placed in a nonvital center such as the lumbar cord

In a series of experiments the relative effectiveness of antitetanic serum when it is administered by various routes was studied It was found that the intrathecal route is more effective than any other in animals with early, mild or moderate symptoms In animals with very severe symptoms no form of therapy and no amount of antitoxin availed to save life This result is in keeping with the observation that once a lethal quantity of tetanus toxin has been fixed by the central nervous system no amount of antitoxin will prevent death It must be borne in mind however that severe symptoms can result from the fixation of less than a full lethal amount of toxin Consequently the presence of tetanic convulsions does not justify a physician in withholding vigorous treatment

Our concept of the pathogenesis of tetanus is that the organisms multiply in necrotic tissue or in the presence of concomitant infection The presence of spores of *Clostridium tetani* in a sterile wound will not cause tetanus When multiplying the clostridia liberate a water soluble substance that diffuses through the adjacent skeletal muscles and acts on the neuromuscular end organs to cause a state of maintained contraction This may persist for months after which time the muscles return to a normal state Some of the toxic substance pas es into the lymphatics and blood stream from which a part is taken up by the specifically reactive cells in the cord and medulla and in the motor end organs of the skeletal muscles In the central nervous system the toxin is probably altered to form a secondary substance that is not neutralized by antitetanic serum This secondary substance circulates in the blood stream and seems to cause death by interference with some essential part of the respiratory mechanism Once a lethal amount of this hypothetical toxin has been formed no known treatment will save the life of the animal

Symptoms —*Types* —There are two main forms of the disease in man generalized

tetanus and localized tetanus In most cases the former alone is recognized, although if carefully sought for, one can find a fair number of patients showing both forms Instances of *local tetanus* occurring without any generalized seizures have become increasingly frequent following the prophylactic use of antitetanic serum This occurs because the quantity of antitoxin sometimes is sufficient to neutralize the toxin in the blood but insufficient to counteract the toxin bound in the tissues near the site of injury The characteristic manifestation of local tetanus is a persistent and unyielding rigidity of a group of muscles This state may continue for weeks or months and then gradually disappear without leaving any residual change It is less likely to be fatal than other types of tetanus *Cephalic tetanus* is the name given to the particularly severe form resulting from injuries about the head *Tetanus neonatorum* is self explanatory

Incubation Period—In most patients this period is usually from five to ten days Occasionally it may be as short as three days or as long as three weeks In many instances it is impossible to determine the time of the initial infection Occasionally generalized tetanus develops despite the administration of a prophylactic amount of antitetanic serum When this occurs the incubation period is usually from two to three weeks

Premonitory Symptoms—In man the presenting symptom of tetanus is usually stiffness of the jaw Frequently this is the only early symptom although restlessness irritability stiffness of the neck difficulty in swallowing may herald the onset of the illness Stiffness of the arms or legs headache convulsions fever or chilliness are occasionally the initial evidences of the disease The importance of assuming that stiffness of the jaw is due to tetanus cannot be over emphasized It is always wise to act as if this is so until some other cause for the stiffness is shown to exist

Later Symptoms—As the disease progresses the muscles of the neck and back become rigid and the stiffness in the jaws is replaced by actual difficulty in opening them This condition called trismus is rendered more marked by reflex stimulation when the patient attempts to eat or drink The face assumes a characteristic expression the so called sardonic smile (risus sardonicus) which results from spasm of the facial muscles and the involuntary raising of the eyebrows The abdominal and lumbar muscles may assume a completely rigid state The contraction of the back muscles is often so great that opisthotonos occurs The rigidity of the abdominal muscles has occasionally led to errors in diagnosis One of the most characteristic features of general tetanus is the development of painful convulsions These are precipitated by relatively slight stimuli such as jarring of the patient's bed or an unexpected noise Profuse sweating accompanies the seizures and the viselike constriction of the chest muscles renders the patient unable to cry out Dysphagia is usually present and interferes seriously with nutrition Cyanosis and asphyxia sometimes result from spasms of the respiratory muscles or glottis The pulse and respiratory rates are increased and the temperature commonly rises from 2 to 5° F Death sometimes occurs from spasm of the respiratory muscles More frequently however the immediate cause of death is not apparent There is frequently sudden termination of breathing although the heart continues to beat for several minutes

Differential Diagnosis—Ordinarily the diagnosis of tetanus is not difficult Confusion occurs only in the initial stages of the disease when stiffness of the neck muscles *or of the jaw might be attributed to* some other condition The early symptoms of meningitis sometimes simulate the beginning of tetanus An impacted and infected third molar tooth may cause trismus Rarely peritonsillar abscesses and cellulitis may cause mild spasms of the glottis and throat muscles which to the uninitiated might suggest tetanus The typical position assumed by the hands and feet in the spasms of tetany rarely gives rise to confusion with the tonic contractions of tetanus In tetany there is no involvement of the jaws or lumbar muscles Strychnine poison at times closely resembles tetanus but rarely involves the muscles of the jaw and in strychnine poisoning the muscles of the trunk and neck are relaxed between spasms

Prognosis—The outlook in cases of generalized tetanus is always grave even in the best hospitals the death rate is frequently

more than 50 per cent There is one group of patients for whom no form of treatment will prevent a fatal outcome There is another group who will recover without specific therapy There is an intermediate group in whom the issue of life or death is determined by prompt diagnosis and adequate treatment When the incubation period is more than nine days the prognosis is rather favorable A more reliable indication however is the length of the interval between the initial symptoms and the occurrence of convulsive seizures The longer this period is the better the prognosis When a patient develops tetanus in spite of having had a prophylactic injection of antitetanic serum the course of the disease is likely to be mild and the chances of recovery very good

Prophylaxis —*Passive Immunization* —The efficacy of prophylactic injection of 1500 units of antitetanic serum is clearly demonstrated in the figures quoted in a preceding paragraph on the incidence of the disease The use of antitetanic serum has prevented the development of hundreds of cases of tetanus but it is not an entirely satisfactory procedure largely because there is no way of telling whether or not one should give antitoxin for a particular injury Every surgeon has had the experience of seeing tetanus develop from a seemingly insignificant wound yet one hesitates to give antitetanic serum to every person with a trivial injury because of the frequently severe reactions that follow the use of serum In addition to malaise serum sickness and anaphylactic reactions instances of peripheral nerve palsies have been reported Furthermore passive immunization with antitetanic serum lasts for only a week or ten days Consequently in cases of severe injury or secondary operations it is necessary to repeat the injection

A common mistake in the use of antitetanic serum is that the dosage is frequently calculated in proportion to the age of the patient Obviously this is a mistake because a small child may have a wound harboring *Clostridium tetani* and producing a great amount of toxin and an adult may have a wound with few organisms producing very little toxin Consequently since antitetanic serum is given to neutralize the toxin formed in a wound the dosage should not be proportional to the age of the patient During the first World War it was customary to give the second dose of antitoxin while the patient was under general anesthesia It seems that this procedure lessens the chance of occurrence of severe reactions Finally the cost of antitetanic serum is a real deterrent to its use Some municipalities provide practitioners with the serum for indigent patients but often the cost of the injection has to be borne by the doctor

Active Immunization —Active immunization against tetanus has been thoroughly studied during the past decade by Ramon and his associates at the Pasteur Institute The medical profession of all countries except France was slow to appreciate the importance and effectiveness of this procedure The Second World War however afforded the stimulus necessary to awaken a very keen interest in it Two kinds of tetanus toxoid have been prepared the plain and the alum precipitated In the United States standards for the potency of each have been set by the National Institute of Health The alum precipitated toxoid appears to produce a better antitoxin response in the patient The method of administering tetanus toxoid is as follows

An initial dose of 1 cc is given subcutaneously In most instances this produces no appreciable amount of antitoxin in the blood At an interval of from one to three months later a similar injection is given and within ten days there is detectable antitoxin in the blood The amount of this antitoxin is practically always sufficient to protect against an ordinary infection If however a third injection of toxoid is given at an interval of from one to three months the titer of antitoxin in the blood rises rapidly and persists for months The exact period for which protection is afforded by three injections of toxoid is not accurately known because this substance has not been available long enough Numerous authors have reported the presence of appreciable amounts of antitoxin in the blood of patients months after a basic course of toxoid has been given

Unfortunately there is no rapid method of measuring a patient s immunity against tetanus at present it is necessary to carry out a bio assay of the patient s serum in guinea pigs This is time consuming and ex

pensive Furthermore we do not know the minimal amount of antitoxin in the blood that will afford certain protection It is known, however that a prophylactic dose of antitetanic serum gives ample protection in the great majority of injuries and that the titer of antitoxin in the blood of an average adult following the usual dose of 1500 units of antitoxin is from 0 1 to 0 2 of a unit It would seem, *therefore* that such a level gives fair assurance of adequate protection Following the production of a state of active immunity it is very likely that the level of circulating antitoxin is not an accurate indication of the existing tissue immunity It is entirely possible that a patient who has had a basic course of three injections of toxoid might after some time not have any detectable *antitoxin in his blood nevertheless* this patient would probably have adequate immunity It is certain that the ability of such a patient to produce large amounts of antitoxin quickly following a fourth injection of toxoid is suggestive of an existing immunity

Reactions —All of the early workers in the field of active immunization against tetanus reported either no reactions or an exceedingly small percentage of reactions following the use of toxoid For instance Whittingham reported that only fourteen reactions of any kind were noted following the immunization of 61 000 soldiers two of these *fourteen reactions were anaphylactic* and twelve were classed as constitutional Gold found only two cases of urticaria occurring in *1700 patients immunized with* alum precipitated toxoid During the summer of 1941 however an altogether unexpected outbreak of severe reactions appeared In some places the incidence was as high as 25 per cent These reactions followed the injection of both the plain and the alum precipitated toxoid and occurred *after* the first as well as after subsequent injections An intensive study was undertaken to determine the cause of this unfortunate occurrence It has become apparent that the use of incompletely digested peptone in the media growing the *Clostridium tetani* was responsible for these reactions The technique of Brewer provides a highly potent toxin practically free from proteins

Results —The war which has now spread around the world has already afforded indisputable proof of the effectiveness of active immunization with tetanus toxoid Practically all the soldiers and horses of the French fighting forces were protected before hostilities commenced Only one soldier is known to have developed tetanus and his case was described as of mild local character Following the campaign in Flanders *there were eight British soldiers in whom* clinical tetanus was recognized These eight were in a group of 1800 wounded who had elected to omit injections with toxoid Among 16 000 who were similarly wounded but immunized not a single instance of tetanus was recorded Finally, it must be emphasized that tetanus is a preventable disease The importance of immunizing children farmers artisans and military personnel *cannot be overemphasized*

Treatment —Every effort must be made to establish the diagnosis of tetanus at the earliest possible time and to commence treatment as soon as it is certain that the patient is not hypersensitive to horse serum Patients with suspicious trismus should be admitted to a hospital and examined at frequent intervals

There are *three main objectives* in the treatment of tetanus *first* one must make every effort to prevent additional toxin from reaching the central nervous system, second the source of toxin must be removed third *the patient must be given rest* To accomplish the first purpose one should give an initial intravenous injection of 50 000 units *of antitetanic serum for the purpose* of neutralizing all of the toxin in the body which is still free and unaltered Obviously it is impractical to try to estimate how much toxin is present in any given patient but 50 000 units of antitetanic serum are sufficient to counteract the toxin in any patient who *has a chance of recovery* It seems unnecessary to give enormous doses of antitoxin for it has been shown experimentally that if one full lethal dose has been fixed and altered by the central nervous system a million neutralizing doses of antitoxin will not save the animal It must be emphasized *however that one cannot* tell whether the symptoms of central nervous system intoxication are due to a fraction of a lethal dose or to several such doses Therefore it is

imperative to give a fairly large initial intravenous dose of antitoxin and thereafter to give daily injections of 5000 units to insure the neutralization of any additional toxin that may be absorbed At the time of the intravenous injection it is important to give an intrathecal injection of from 15 000 to 20 000 units of antitetanic serum With children or with patients having severe opisthotonos it is wise to do this under general anesthesia The serum may be given either by lumbar puncture or intracisternally and of course should be administered slowly Severe and fatal reactions following the intravenous or intracisternal injection of serum have been described In none of our animals has such a reaction occurred nor has Vener reported fatal reactions in any of the seventy five patients he treated with intrathecal injections It is highly desirable that a more refined and stronger antitetanic serum be prepared to minimize the possibility of untoward reactions

Following the intravenous treatment the tissues around the infected wound should be infiltrated with approximately 10 000 units of antitetanic serum in preparation for *wide excision of the wound* This excision should be done an hour or so later and the wound left open The saturation of the tissues adjacent to the wound with antitoxin effectively prevents the dissemination and absorption of toxin at the time of operation

The *control* of *convulsive seizures* in tetanus is always a major problem The suggestion that this be accomplished by the use of sufficient amounts of chloral paraldehyde or ether oil per rectum is based largely on experimental work For certain species it seems clear that drugs which are respiratory depressants shorten the life of animals having tetanus Surprisingly large amounts of paraldehyde (from 10 to 40 cc per rectum every three hours) can be given to human beings without harm When necessary the drug can be administered in normal salt solution by the continuous intravenous drip method There are a few cases of tetanus in which death is due to laryngeal spasm When severe stridor occurs it is wise to perform a tracheotomy and if necessary maintain respiration by artificial means The use of an oxygen tent is of benefit in all severe cases of the disease

It is of fundamental importance of course to see that patients with tetanus are kept in fluid and electrolytic balance and that they are given adequate nourishment To do this it is often necessary to depend upon a liquid diet of high caloric value Frequently this has to be administered by an indwelling gastric tube passed through the nares

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TYPHOID FEVER

Definition —Typhoid fever is an acute generalized infection caused by the *Eberthella typhosa* Pathologically the lymphoid tissues of the body show the greatest changes there are hyperplasia and ulceration of Peyer s patches and the solitary lymph follicles of the intestinal tract swelling of the mesenteric lymph nodes and spleen The clinical manifestations variable in degree are high fever slow pulse a rose-colored eruption abdominal tenderness and enlargement of the spleen

History —A continued fever associated with delirium has been recognized since the time of Hippocrates but not until 1820 was it recognized as a disease entity when Bretonneau studied an epidemic in Tours and first described the intestinal lesions Louis in 1829 gave a description of the disease and the name 'Fievre Typhoide" To a group of Americans great credit is due for distinguishing typhoid fever from typhus fever W W Gerhard of Philadelphia a student of Louis had the opportunity of observing an

epidemic of typhoid and typhus fever and in 1837 published in the American Journal of Medical Sciences an article which clearly differentiates these diseases Credit is also due Alfred Stillé George Shattuck and James Jackson Senior and Junior for having further popularized the existing knowledge of this disease Budd in the years 1856 to 1860 published in the Lancet for the first time that the infective agent was in the stools In 1880 Eberth discovered the specific cause of the disease and in 1895 Widal brought the agglutination reaction of Pfeiffer into prominence as being of value in the diagnosis of typhoid

Incidence —The disease is universally distributed occurring in practically all parts of the world In former years it was a very prevalent infection during the summer and early autumn months in the most populated areas of the temperate climates Contaminated water and infected food are its chief sources Fingers food and flies frequently account for its local distribution in homes and hospitals During the past twenty five years there has been a marked decrease in the incidence and death rate of this disease In 1910 in 78 American cities with a total population of 22 573 435 the death rate was 20 54 per 100 000 In 1940 in the same cities with a total population of 35 895 038 the death rate had fallen to 0 48 per 100 000

Typhoid fever has been one of the greatest scourges of armies and during the Spanish American War among 107 973 men in the national encampments there were 20 738 cases of typhoid with 1580 deaths In the South African War in the British army of 557 653 there were 57 684 cases of typhoid with 8225 deaths During the World War the American army consisting of more than 4 000 000 men had only 227 deaths from typhoid fever This record is a great tribute to the efficiency of modern sanitary methods and of prophylactic immunization against the disease

Season —The maximum number of cases occurs in the autumn with a slight variability according to location A rise in the prevalence of the disease is noted in July extending through August and September and decreasing in October

Age —Typhoid fever is distinctly a disease of youth and early adult life occurring with greatest frequency between the ages of fifteen and thirty years It is rare in infancy and in the elderly Males and females are equally susceptible

Immunity —Not all persons exposed to the infection contract the disease After recovery a partial immunity develops but second attacks are not uncommon An acquired immunity can be produced in most persons by the subcutaneous injection of increasing doses of killed cultures of *E typhosa*

Bacteriology —The *Eberthella typhosa* is a short actively motile aerobic organism with rounded ends growing readily at body temperature in all culture media particularly well in milk which it does not coagulate It is a gram negative bacillus and does not ferment lactose or dextrose When grown on bismuth sulfite media the typhoid colony has a black metallic sheen whereas the colon bacillus colonies are white *Salmonella paratyphi* and *S schottmulleri* colonies have a green color The bacillus is killed when exposed to a temperature of 60° C for ten minutes it may live for months at a temperature below freezing The ordinary disinfectants such as carbolic acid 1 20 solution and bichloride of mercury 1 1000 solution are quite efficacious in killing the organism Park found that when *E typhosa* are dried the majority of them die within a few hours a few may survive for several weeks or months Direct sunlight kills most of them after exposure for several hours but they may live several days in water

Etiology —*Entrance to the Body* —The *E typhosa* gain entrance directly through the gastro intestinal tract Entering supposedly through Peyer s patches and the solitary lymph follicles they pass to the mesenteric lymph nodes and from this point through the thoracic duct into the blood stream After entering the blood they are distributed into every organ of the body During the first week of the disease the organisms are easily recovered from the blood and in a few patients they can be isolated from the urine and feces however as the disease advances the organisms usually disappear from the blood stream and are recovered in an increasing number of cases from the urine and stools The site of greatest multiplication of the bacilli is probably the biliary system since *E typhosa* are recovered in greater numbers from the duodenal contents and diminish in frequency as the lower intestinal tract is reached They

are eliminated from the body through the urine and feces Approximately 75 to 85 per cent of positive cultures are obtained from the blood during the first week of the infection From the second to the third week stool cultures are positive in a high percentage of cases As recovery takes place the organisms first disappear from the blood and later from the urine and feces

Modes of Infection—Every patient with typhoid fever should be regarded as a source of infection for the spread of the disease and since the organisms are easily destroyed by proper disinfection of the excreta it is necessary to adopt strict measures to prevent the spread in households hospitals and communities

Water—Infected water is by far the most common source of widespread epidemics Statistical studies made in this country have shown that this is a prevalent source of infection The steady decrease in the incidence of typhoid fever in communities where the water supply is improved is the best evidence that many cases are due to water borne infection

Food—Milk is the next most important source of infection many epidemics have been traced directly to this article of food Contamination of food may occur by washing utensils with infected water or by contact with flies previously contaminated with the excreta of typhoid patients but most frequently it is infected by contact with the hands of typhoid carriers All uncooked vegetables may be possible sources of infection butter and cheese are very rarely so Oysters and other shellfish may convey the disease if they live or are fattened in infected streams

Carriers—Every person recovering from typhoid fever should be considered a carrier until repeated stool and urine cultures fail to show *E typhosa* The organism may be present in the stools for months or years after the patient has completely recovered from the disease Occasionally perfectly healthy individuals who give no history of having had typhoid fever are found harboring the E typhosa bacillus About 80 per cent of the carriers are women Carriers who come in contact with food are particularly dangerous Typhoid Mary a cook was the first recognized typhoid carrier in the United States She caused at least ten out breaks of typhoid with at least fifty-one persons infected Recent study has shown the value of Vi aggglutination to determine carriers The Vi agglutinin apparently occurs only in those persons suffering with actual typhoid fever or who are harboring these organisms and can therefore be used as a successful screen test in the detection of carriers The use of sulfonamides in the treatment of carriers has not as yet proved of any lasting value

Pathologic Anatomy—The most characteristic changes to be observed in typhoid fever are found in the intestinal tract The Peyer s patches and solitary glands are the places where the typical changes are first seen they become red and swollen and project above the surface of the bowel The ordinary lymphoid tissue is replaced by an enormous number of large mononuclear phagocytes and there is almost a complete absence of polymorphonuclear leukocytes in these areas These large cells to which attention was particularly directed by Mallory are probably endothelial in origin and come from the reticulo endothelial system By the end of the first week or ten days due to engorgement of the vessels and perhaps pressure from the accumulation of endothelial cells the blood supply to Peyer s patches is interfered with and there begins on the surface of the swollen patch a superficial necrosis which as it progresses forms an ulcer The ulcers are usually round or slightly oval with the long axis corresponding to the long axis of the bowel Contiguous ulcers may coalesce especially near the ileocecal valve so that the lower ileum presents the picture of one large ulcerated area The cecum and proximal part of the colon are involved in about one third of the cases The size and number of ulcerations bear no relation to the severity of the disease indeed the ulceration is not a fundamental part of the pathology of typhoid fever—patients may die from the toxemia of the disease and at autopsy show very few or no lesions in the intestine Healing takes place without the formation of cicatricial tissue the ulcers being covered by a simple epithelium without glands The mesenteric lymph glands in the involved areas particularly those which drain the lower ileum are hy

peremic, sometimes quite soft, and frequently hemorrhagic The same changes are observed in the lymph nodes as in the Peyer's patches, namely, the engorgement of the sinuses by large mononuclear phagocytic cells similar to those seen in Peyer s patches Necrosis may take place with rupture of the gland into the peritoneal cavity

Spleen—As a rule the spleen is enlarged Sometimes its weight may reach 600 to 700 Gm which is three to four times that of a normal spleen It is soft and on microscopic examination shows an accumulation of large endothelial phagocytes Rupture may occur spontaneously or as a result of injury producing a peritonitis

Liver—There is usually cloudy swelling of the liver and also small areas of focal necrosis These necrotic areas may resemble small tubercles but on close examination they are found to be an accumulation of the large endothelial cells which have blocked sinusoids and caused necrosis MacCallum believes that the liver cells are not involved but are merely pushed aside by the phagocytes Since bile greatly enhances the growth of the typhoid bacillus the gall bladder is invariably infected Acute cholecystitis is not rare and occasionally typhoid ulcers have been found in the wall of the gallbladder

Kidneys—The kidneys show cloudy swelling the result of the action of toxins on these organs While there is usually a bacilluria cystitis and pyelitis are uncommon

Respiratory Organs—The lungs may be the seat of pneumonic consolidation which may be of either the bronchial or lobar variety This is usually secondary, very rarely does the *E typhosa* cause a pneumonia Bronchitis is a common early symptom Abscesses and gangrene may develop as well as infarcts

Muscles—There is usually a hyaline degeneration of muscles in which the fibers lose their transverse striation Those most commonly involved are the muscles of the thighs arms and diaphragm

Cardiovascular System—Endocarditis is quite rare though there have been cases reported in the literature Pericarditis due to the *E typhosa* is almost unheard of The most frequent change in the circulatory system is an extremely soft flabby myocardium in which many of the fibers have lost their striation Fatty degenerative changes in the arteries do occur but these are not specific for typhoid The lesions are usually located in the intima or media and it is possible that many of the sudden deaths in typhoid are the result of degenerative arterial changes Arterial thrombosis is rare but thrombophlebitis is quite common especially in the left femoral vein

Nervous System—Very few changes are made out Meningitis is rare, optic neuritis sometimes occurs Parenchymatous changes have been observed in the peripheral nerves even when there were no particular symptoms of neuritis

Symptomatology—The incubation period is quite variable and may last from five to forty days The average is from ten to fourteen days During this stage there are few or no symptoms although if careful observations are made the temperature might show a slight elevation in the evening The onset is rarely acute and it is with a great deal of difficulty that a patient can state a definite beginning Chills or chilly sensations alternating with hot flashes occur fairly frequently Headache, backache anorexia diarrhea epistaxis and constipation with generalized aching usually constitute the outstanding prodromal symptoms Bronchitis is frequent often it is quite misleading particularly when associated with a leukocytosis, which is not an infrequent observation It is usually a generalized condition that clears up within the first week or ten days of the disease

Fever—It is rare that an individual becomes infected with the *E typhosa* without having fever although during epidemics positive blood cultures are at times obtained from those who are in contact with the disease but who exhibit no clinical manifestations

The usual febrile response in typhoid is characterized for purposes of description by three phases first the rise second the period of continued fever third the fall During the first week of the infection there is a gradual daily increase in the height of the fever which rises in a steplike manner until at the end of a week or ten days it has reached a level of 103° or of 104° F The second phase is the period of continued fever

in which the daily remissions are very slight but which lasts for ten days to two weeks The third period, that of defervescence begins about the third week and lasts for seven to ten days in this period the daily fluctuations are most marked and resemble those of a septic infection

Not all patients with *Eberthella* infection run such a typical temperature curve and in those with quite severe infections the temperature may be quite irregular Sudden changes in the temperature unless caused by hydrotherapy or drugs should make one suspicious of complications After a large hemorrhage the fever may drop 6° or 8° F After perforation there may be an initial fall of fever followed by a rise During convalescence there is a tendency for the temperature to be subnormal

Pulse—The pulse in typhoid presents two characteristics—its relative slowness in comparison with the height of the temperature and the fact that it is dicrotic These characteristics are among the earliest and most suggestive aids in diagnosis A pulse rate of 80 to 90 with a temperature of 103° to 104° F is not uncommon Many patients have gone through typhoid fever with a pulse rate of less than 100 Dicrotism which is not as common in children as in adults may persist during the entire course of the disease and extend well into convalescence but as a rule it disappears during the third week A persistently rapid pulse early in the disease signifies a rather severe infection and marked toxemia

Skin—The rose colored rash which is usually described as typical of typhoid fever makes its appearance from the seventh to the tenth day It is observed most commonly upon the abdomen but may appear on the chest and back It consists of small round elevated rose colored areas from 2 to 4 mm in diameter that disappear on pressure This rash usually comes in crops and after persisting for two or three days it disappears occasionally leaving a brownish stain In some patients the eruption may be quite abundant and in the white race it is seen in approximately 90 per cent of the patients Herpes is extremely rare Sudamina occurs with considerable frequency Areas of superficial gangrene may develop particularly after the prolonged use of ice packs Swelling or edema of the skin occasionally occurs but most commonly as a result of thrombosis of a femoral vein Sometimes with the onset of nephritis edema is seen The occurrence of bed sores is quite rare and is usually due to negligence on the part of the nurse although in the days when typhoid patients received a very low caloric diet pressure over the sacrum was usually sufficient to produce acute decubitus ulcers in some patients

Nervous Manifestations—Headache of a very severe character is a fairly frequent initial symptom Pain is usually located in the frontal region most commonly bitemporal Sometimes this constitutes a very distressing symptom although as a rule the pain is of a dull uncomfortable continuous character Convulsions when they occur are most commonly observed in young children Delirium listlessness photophobia twitching of the muscles and somnolence are usually indications of a severe infection Sometimes the headache and stiffness of the neck would lead one to suspect meningitis

Gastro intestinal Tract — Occasionally nausea vomiting and diarrhea are observed sometimes there is marked abdominal distention associated with the diarrhea Such symptoms in the beginning of typhoid fever are usually brought about when very little attention is paid to dietary regulation or when a purgative is given at the onset of the illness The spleen is practically always enlarged except in individuals of the colored race It becomes palpable about the end of the first week of the disease but seldom extends over 3 cm below the costal border

Blood—As a rule there is a rather marked leukopenia in typhoid fever The average count will vary from 3000 to 5000 white blood cells per cubic millimeter The decrease in the number of leukocytes is accounted for by a diminution in the number of the neutrophilic cells As the disease advances there is a gradual decrease in the number of red cells and an equivalent decrease in the hemoglobin The systolic and diastolic blood pressures gradually fall during the course of the disease and in persons with a normal blood pressure this may amount to as much as 10 to 20 mm of mercury

Chills—Chills may occur at the onset of

the disease, and they may recur throughout the course of the disease without explanation However, they usually mark the onset of some complication, or follow the administration of an antipyretic Sometimes they are associated with constipation

Epistaxis is one of the early symptoms and occurs more frequently in typhoid fever than in any of the infectious diseases It may be profuse and serious and recur frequently during the course of the illness

Bronchitis is a frequent initial symptom and may be accompanied by a severe or distressing cough On physical examination there are many sibilant rales over the chest Pneumonia and atelectasis occasionally occur

Renal Symptoms—Albuminuria is a common finding particularly during the febrile stage This, as a rule is accompanied by the presence of a few casts As the temperature subsides and the toxemia diminishes the albuminuria gradually disappears *E typhosa* occur in the urine in approximately 40 per cent of patients Occasionally nephritis of the acute variety is observed Pyelitis may involve one or both kidneys occurring either in the early stages or during the height of the disease Perinephritic abscesses are rare

Relapse—This usually occurs after the patient has had a normal temperature for five to ten days As a rule it is a much milder infection and runs a shorter course than the original disease although occasionally it may be more severe Infrequently more than one relapse occurs The onset is usually without warning and is accompanied by the usual signs and symptoms of typhoid fever The rose spots reappear the spleen which was at one time palpable is easily felt again the temperature rises but is usually not as high as on the former occasion Relapse may last from one to three weeks The causes of relapse are purely speculative but they have been most commonly attributed to dietary indiscretion however proof for such a theory is lacking

Complications—Intestinal hemorrhage is one of the most serious complications The bleeding may vary in intensity from that which is detectable *only* by chemical means to an extensive massive hemorrhage which may completely exsanguinate the patient No relationship can be found to exist between the severity of the disease and the frequency or severity of intestinal hemorrhage Severe hemorrhage may occur in a very mild infection whereas a severe case may have no hemorrhages at all It is a serious complication and occurs usually in about 6 to 7 per cent of all cases it is most commonly observed during the third week of illness and comes as a rule without warning The first evidence of its occurrence may be a sudden drop in the temperature or a marked increase in the pulse rate accompanied by pallor chilliness sweating and anxiety on the part of the patient The bleeding is a result of the erosion of one of the small or medium sized arteries situated in Peyer s patches The occurrence of intestinal hemorrhage markedly increases the seriousness of the prognosis about 20 per cent of those who develop this complication succumb to the disease

Perforation—This is by far the most important the most dreaded and most fatal complication of typhoid fever In a great majority of instances it occurs during the third week in the severe cases particularly those associated with diarrhea, tympanites and hemorrhage The most common site of the perforation is the lower portion of the ileum As a rule the perforation occurs singly but there may be more than one opening in the intestine The actual cause is usually abdominal distention or the result of vomiting or straining at stool

By far the most important single symptom is a sudden sharp pain referred to the *lower right abdominal quadrant* sometimes it may be diffuse and detected only by deep pressure in the abdomen Shortly after the onset of pain a decided change is observed in the condition of the patient—there is nausea and vomiting the pulse increases in rate the temperature usually falls *to be* followed by a rise there is local rigidity of the abdominal muscles particularly near the site of perforation and after a short space of time the entire abdomen becomes markedly rigid Distention may or may not occur If gas escapes into the abdominal cavity the liver dulness becomes obliterated If there has been a leakage of fluid into the abdominal cavity it can be detected by the presence of a friction rub over the splenic or

hepatic areas or by the demonstration of shifting dulness in either flank With the perforation there is usually an increase in the leukocytes although this sign cannot always be relied upon as a *sine qua non* for the reason that unless the leukocyte count is known before the perforation occurs a slight rise cannot be appreciated However if several counts are made in the course of three or four hours it will be observed that there is a steady increase in the number of white cells It is difficult to distinguish between an acute cholecystitis acute appendicitis rupture of a mesenteric lymph node and intestinal perforation In a patient presenting symptoms of such a lesion it is much better to advise an exploratory laparotomy rather than delay too long for the development of a perfectly typical picture Even under the most favorable conditions the mortality is distressingly high

Cholecystitis—Acute cholecystitis is a rather rare complication of typhoid fever When we remember that the bile is a favorite medium for the growth of *E typhosa* it seems strange that the gallbladder is not involved more frequently in an inflammatory process Suppuration however may occur and when it does is similar to the symptoms which are observed in an acute cholecystitis from any other cause The *E typhosa* grows well in any medium that contains bile so that it is not unusual to find that the bile still contains this organism after complete recovery from typhoid fever

Thrombosis—This is usually a late complication of typhoid occurring in the majority of cases after the fourth week and frequently during convalescence The femoral vein on the left side is more frequently involved than any other This complication is ushered in usually with a chill increase in fever and pulse rate with soreness or pain over the involved vein The fever and pain usually increase for two or three days at the end of which time the involved blood vessel may be palpated as a very tender superficial cord Accompanying this there are usually swelling of the extremity an increase in the number of leukocytes but seldom any marked circulatory change in the limb A grave danger following thrombosis is a possible dislodgment of the clot causing pulmonary embolism and sudden death

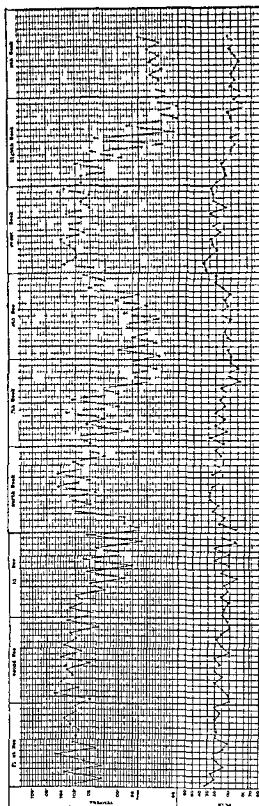


Fig 20—Temperature and pulse record of a twelve-year-old boy with typhoid fever The temperature began to drop at the end of the third week At the beginning of the fourth week he had a recrudescence At the end of the fifth week his temperature again came down but rose again during the sixth week, when he developed a relapse which lasted almost two weeks During the seventh week the blood culture was again positive for *E typhosa*.

Respiratory System—*Epistaxis* is quite common at the onset particularly in children

the disease and they may recur throughout the course of the disease without explanation However, they usually mark the onset of some complication or follow the administration of an antipyretic Sometimes they are associated with constipation

Epistaxis is one of the early symptoms and occurs more frequently in typhoid fever than in any of the infectious diseases It may be profuse and serious and recur frequently during the course of the illness

Bronchitis is a frequent initial symptom and may be accompanied by a severe or distressing cough On physical examination there are many sibilant rales over the chest Pneumonia and atelectasis occasionally occur

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or premature labor in approximately 60 per cent of the patients

Diagnosis —The diagnosis of typhoid fever may be one of the easiest or one of the most difficult problems which a physician encounters The clinical findings are of greatest significance the history of gradual onset with malaise epistaxis headache drowsiness bronchitis increasing temperature from day to day a slow pulse dicrotic in character roseolar skin eruption and an enlarged spleen is quite suggestive If these symptoms can be connected with a recent trip to a known typhoid area they become of greater importance A leukopenia is of considerable significance although it does occur in other diseases

Blood Culture —A culture from the blood should be made from every suspected case in which there is continued fever During the first week of the disease the *Eberthella* organism can be recovered in approximately 85 per cent of the patients As the disease advances positive results become less frequent

Cultures from Urine and Feces —During the first week of the illness positive cultures may be obtained in approximately 10 per cent of patients as the disease progresses the organism is obtained with greater frequency by the end of the third week 80 per cent of typhoid patients yield positive cultures in the excreta

Widal Reaction —When blood cultures cannot be made the Widal test is of considerable importance for it is positive in some stage of the disease in practically all cases This reaction is based on the presence of specific agglutinins for the *E typhosa* in the patient s blood and was first utilized by Widal as a method of diagnosing typhoid fever This reaction is usually not positive until the second week and in some cases several tests must be done before a positive result is obtained Agglutination with a dilution of the patient s serum in a strength of 1 50 or 1 100 is considered positive Widespread use of prophylactic injections of typhoid vaccine has lessened to some extent the diagnostic value of this test If the reaction continues to be positive with a rising dilution of serum it is of considerable importance in making the diagnosis

Differential Diagnosis —Many diseases may simulate typhoid fever so that it will not always be possible to make a positive diagnosis within the first five or six days of the infection Keeping in mind the general clinical picture of the disease with help afforded by blood urine and stool cultures and the Widal reaction it is generally possible to make a positive diagnosis The diseases most frequently giving difficulty are

Malaria —At times malaria particularly the estivo autumnal type may be confused with typhoid fever In malaria the daily fluctuation of the temperature is more marked chills occur with greater frequency and irregularity The spleen is usually larger and firmer and the parasites can usually be demonstrated in the blood On occasions it may be necessary to give at least 30 grains of quinine a day for three or four days as a therapeutic test Atabrine may be used for the therapeutic tests instead of quinine giving 1½ grains (0 1 Gm) three times a day for three days

Miliary Tuberculosis —In this disease, especially when there are no localizing symptoms the differentiation from typhoid fever may be extremely difficult Both have an insidious onset both may be characterized by prolonged fever bronchitis malaise anorexia gastro intestinal symptoms and a positive Widal reaction A familial history of tuberculosis is of help The pulse and temperature ratio so commonly seen in typhoid fever are not observed in this form of tuberculosis The pulse rate is faster seldom dicrotic the respirations are increased and the temperature curve is much more irregular than in typhoid While leukopenia may be present a slight leukocytosis is more common In miliary tuberculosis there is cyanosis of the lips and fingertips coughing and localized signs in the lungs or in the central nervous system An x ray examination of the chest together with serologic studies of the blood and culture from the stools will help greatly in the differentiation

Bacterial endocarditis is usually distinguished with ease although in some cases considerable difficulty may exist. The fever in this condition is seldom so continuous or so high as in typhoid Frequent and irregular chills with a septic type of temperature are much more common The presence of petechiae in the conjunctivae is of much impor

and young adults *Bronchitis* is frequently seen in the early stages of the disease and in the majority of cases is characterized by severe coughing *Catarrhal laryngitis* is occasionally seen and may be associated with extensive ulceration the ulcerative lesions sometimes developing so slowly that they escape recognition until edema occurs Unusual hoarseness tickling sensation in the throat and loss of voice should be symptoms which warn of the development of this condition *Pleurisy* is rather rare in typhoid fever but it may occur at any period of the disease as a primary condition or secondary to some other lesion such as pneumonia or infarction It is usually fibrinous but in a few instances it may become purulent *Lobar pneumonia* is infrequent It is usually caused by the pneumococcus although the *E typhosa* occasionally may be the causative agent *Bronchopneumonia* occasionally develops during the course of the disease, it usually occurs in delirious patients and is sometimes brought on by aspiration of foreign material *Infarction of the lung* may occur as a result of the dislodgment of a thrombus from the femoral vein

Circulatory Complications —Degenerative changes in the heart muscle are fairly common These usually involve the musculature in the form of a parenchymatous degeneration of the fibers Evidence of the existence of such conditions is manifested usually by an increased rate in the pulse lowering of the blood pressure irregularity of the heart and diminution in the intensity of the first heart sound which may be accompanied by a soft systolic murmur Endocarditis and pericarditis are very rare

Nervous System —In a great number of cases headache disturbed sleep delirium particularly at night and tremors—*subsultus tendinum*—are the conditions most frequently observed Stiffness of the neck and suggestive symptoms of meningitis are occasionally observed True purulent inflammation of the meninges is rare Psychoses are sometimes encountered They may appear at any stage of the disease and vary from the manic depressive type to melancholia or mild states of confusion which usually are not serious and disappear during convalescence *Peripheral neuritis* involving the nerves of the lower extremities is fairly common The tender toes' described by Osler are occasionally seen Polyneuritis may occur Convulsions are rare and most commonly observed in children usually at the onset of the disease They may be due to inflammation of the brain or to a marked toxemia

Genito-urinary System —In severe cases with marked toxemia and stupor, retention of the urine is sometimes seen In some patients there may be incontinence without retention Slight albuminuria with a few tubular casts is nearly always noted but actual nephritis is uncommon In nearly all fatal cases there is cloudy swelling with degeneration of the cells of the convoluted tubules of the kidneys Hemorrhagic nephritis is quite rare recovery from the milder irritations of the kidney is the rule *Eberthella* bacilluria is present in 40 per cent of the cases and may persist for many months Cystitis and pyelitis may occur either as a result of infection by the *E typhosa* or from a pyogenic organism Gangrene of the bladder has been observed Orchitis is a rare complication which may occur during convalescence It usually terminates in resolution although at times suppuration takes place

Lesions of the Bones —Periostitis osteitis and osteomyelitis are not uncommon complications They may occur even months after recovery from typhoid fever The tibiae femur, ribs bones of the forearm and clavicle are most often affected Arthritis is occasionally observed it may be monarticular or polyarticular The hip joint is occasionally involved and is sometimes the site of spontaneous dislocation In the absence of suppuration complete recovery with good function is the rule The condition known as typhoid spine depends for its production on an inflammatory lesion involving the periosteum of the bony structure of the spine usually in the lumbar region Sometimes the intervertebral disks are affected It is usually accompanied by pain on motion and tenderness over the spine

Other complications such as parotitis are rare This is usually due to lack of proper nursing care and comes from a mouth which has not had the usual hygienic treatment

Pregnancy associated with typhoid fever is unfavorably affected resulting in abortion

or premature labor in approximately 60 per cent of the patients

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tance and significance Dyspnea, and the presence of a heart murmur, which increases in intensity, joint pains and red cells in the urine are of differential value Infarcts occur commonly in endocarditis The blood culture usually furnishes the conclusive evidence needed to confirm the diagnosis

Pyelitis with high fever although usually not of the continuous type may last from two to three weeks without localizing symptoms and may thus cause confusion A leukocytosis tenderness in the back or over the kidney, together with the presence of pus in the urine serve to establish a diagnosis

Typhus Fever —Formerly these two diseases were frequently confused and even now sporadic cases will sometimes give difficulty As a rule the onset of typhus is rapid and dramatic often with a chill and intense, persistent headache the fever rises rapidly and remains high without remissions, the leukocyte count is elevated, the spleen when enlarged becomes so earlier than in typhoid fever The characteristic rash appears usually on the fifth to sixth day and its extent depends on the severity of the disease The lesions are maculopapular and slightly oval and a few may coalesce They do not fade with pressure and very frequently they have a hemorrhagic center Typhus lasts as a rule two to two and one half weeks and frequently ends abruptly with a crisis Serologic tests for typhoid are negative but in typhus fever there is usually a positive Felix Weil reaction at the end of ten days

Trichinosis —In cases of trichinosis in which there is prostration high fever diarrhea and a rash simulating the rose spots of typhoid, diagnosis may be confusing at the onset As a rule the muscular soreness of trichinosis is much more severe than that in typhoid and is greatly aggravated by motion The blood count usually reveals a leukocytosis and the differential count will show a marked eosinophilia Skin sensitization tests for the *Trichina spiralis* can be tried in doubtful cases

Meningitis —With the sudden onset of typhoid with marked delirium headache and stiffness of the neck there may be present all the signs of acute meningitis including opisthotonos and twitching of the muscles A lumbar puncture and study of the spinal fluid will quickly establish the diagnosis

Syphilitic Fever —In latent syphilis there may occur a long continued fever with constitutional symptoms but with *few or no* manifestations of syphilis The history of a primary lesion, a positive Wassermann and negative serologic tests for typhoid are of value in differentiating the two conditions Sometimes a therapeutic test may be of value

Undulant Fever —Acute infections with the *Brucella* group of bacteria can be differentiated only by recovery of the organism from the blood stream or an increasing titer of agglutinins occurring in the patient's blood

Hodgkin's disease without adenopathy and *osteomyelitis* without localized signs may offer some difficulty A careful history physical examination, and blood counts will be of great help

Prognosis —*The Death Rate* —Deaths from typhoid fever vary considerably from year to year depending in a great measure upon the virulence of the infection Speaking generally the prognosis in the average case is very good The chances for recovery are much better in private practice than in general hospitals This in part, is due to the fact that in private patients the disease is detected earlier and treatment is instituted before the patient becomes seriously ill The average mortality among private patients is about 7 per cent whereas in general hospitals the average rate is approximately 14 per cent It is commonly believed that the general physical condition of the patient before the onset of the disease plays some part in determining the prognosis The mortality is high in infants in people over fifty and in the obese As a rule the most frequent cause of death is toxemia which is evidenced by unusually high fever restlessness delirium and abdominal *distention* Hemorrhage and perforation of course greatly increase the hazard Sudden death sometimes occurs without a reasonable explanation for such a catastrophe It is thought that marked toxemia affecting the heart muscle and causing ventricular fibrillation is the explanation

Prophylactic Measures —It is reasonable to assume that if all *E typhosa* were destroyed as they leave the body the disease

would soon be completely eradicated This problem, however is an extremely difficult one and is the chief cause of the spread of the disease from individual to individual or from an individual by contamination of water or food supplies to communities Hope for the complete eradication of typhoid lies in two directions (1) the early recognition of all patients with typhoid fever, (2) the establishment of rigid measures for the isolation of the patient and the complete destruction of all *E typhosa* from the body

Isolation and the Patient —An individual with typhoid fever need not necessarily be completely isolated provided certain restrictions regarding personal contact and disposal of excreta are strictly observed The screening of a well ventilated room to prevent the entrance of flies is most important After recovering from the disease stool examinations should be made in order to be certain that the patient no longer harbors the *E typhosa*

Disinfection of Stools and Urine —All excreta from the patient particularly the stools and the urine should be promptly disinfected Boiling or treatment with live steam is most efficacious Should this not be feasible the stools and the urine should be deposited in a receptacle to which is added 5 per cent carbolic acid solution or a 10 per cent solution of formaldehyde or perhaps a goodly quantity of quicklime The excreta should be allowed to remain in contact with these disinfectants for two or three hours If the attendant is made to realize that each specimen of stool and urine is a possible source of infection for spreading typhoid fever greater care will be exercised in their complete disinfection

Attendants —All individuals who administer to the typhoid patient should see that after performing any service the hands are washed in a solution of alcohol or cyanide of mercury The bed linen and the clothing worn by each patient should be soaked in a solution of carbolic acid or formaldehyde or be boiled before being sent to the laundry All dishes glasses and utensils that come in contact with the patient during the process of feeding must be properly sterilized by boiling after use Particular attention should be paid to the disinfection of bed pans and urinals

Food and Water —As previously stated the incidence of typhoid fever in a community is a good index of the intelligence of the local health officer A good clean fresh water supply must always be at hand Boiling water or the addition of 15 grains of fresh calcium hypochlorite to 36 gallons of water is sufficient to prevent infection Milk should be carefully protected from flies and dairies should be frequently inspected Milkers or those who handle milk must be known to be free from typhoid infection The pasteurization of milk renders this article of food safe for consumption

Prophylactic Vaccination —Protective vaccination against typhoid fever has amply demonstrated its value as is evidenced by the results obtained in the United States Army during the World War and the more recent report of Col G F Lull in the C C C Camps where 1 400 000 young men received the inoculations and only 237 developed typhoid fever of these 33 had not completed the series of inoculations The vaccine recommended for preventive inoculations contains 1 billion killed *E typhosa* 750 million killed *Salmonella paratyphi* and *S schottmulleri* per cubic centimeter Recent investigation has shown that infection with *Salmonella hirschfeldii* occurs occasionally in this country and is common in South America It therefore seems advisable to use the vaccine containing all four of the organisms to give the widest protection The subcutaneous administration of the vaccine in three doses of 0.5 cc 1 0 cc and 1 0 cc at weekly intervals has been the method used in the past With this method there is occasionally a systemic reaction It is particularly important to be sure that none is given intravenously Recent work by Tuft has shown the effects of the intracutaneous method of typhoid immunization with the complete elimination of annoying reactions The suggested dosage is 0 1 cc 0 15 cc and 0 2 cc of the ordinary combined vaccine given intracutaneously at weekly intervals The use of oral vaccine has not as yet proved of particular value in producing any appreciable immunity and until more satisfactory results have been demonstrated should not be utilized

Siler and Dunham using the mouse protection test for estimating the immunity fur-

nished by typhoid vaccination conclude that a large proportion of immunized persons are protected for a period of two or three years after vaccination They also observed that, using the same method of determining immunity in persons previously immunized the intracutaneous injection of 0 1 cc of typhoid vaccine produces an immunologic response equivalent to that obtained by the previous 3 subcutaneous injections The local and systemic reaction following the intracutaneous injection is relatively mild By employing this method or the subcutaneous injection of 0 5 cc of typhoid vaccine each year individual immunity can be kept at its height During an epidemic or in any household where typhoid fever develops, all exposed individuals should receive prophylactic inoculations

Treatment —In no disease is it more important to have the services of a skilled attendant or nurse than in typhoid fever Fortunately in the past twenty five years the profession has learned that good nursing care is of greater importance than drugs in the treatment of this disease If possible all patients with typhoid should be hospitalized When this is not feasible the patient should be placed in a clean well ventilated room, which has been stripped of its unnecessary furnishings and properly screened Should the services of a nurse not be available then some responsible member of the family should be given the necessary instructions concerning the care of the patient This should consist first and foremost in training and demonstrating how to disinfect thoroughly all excreta bedclothes dishes and anything else which might be contaminated All members of the family should be inoculated During the progress of the disease the nurse should be informed of the complications that may arise and should be instructed to report at once to the physician any unusual happening such as severe abdominal pain tarry or bloody stools a sudden rise or sudden drop in fever or any marked change in the pulse rate

The patient should be in a bed which is properly protected by sheeting to prevent soiling and contamination of the mattress From the outset a regular regime should be instituted and followed Particular attention should be paid to the teeth and the mouth should be kept clean Purgatives of all kinds are to be avoided especially after the first week of the disease A daily bath is not only necessary but it affords ample opportunity for a careful inspection of the patient *Alcohol rubs* are of great value and can be given three or four times daily They are of assistance in keeping the skin in good condition As a rule visitors do much more harm than good If admitted they should be present for only a short time

Diet—In the past patients with typhoid fever have suffered greatly from undernutrition and avitaminosis because of the popular belief that typhoid patients should receive only certain types of food The diets formerly prescribed were extremely limited and poor in caloric value Since the demonstration by Coleman and Shaffer that a patient can go through typhoid fever without marked loss of weight the restrictions previously imposed have been removed and it is now possible to feed the typhoid patient enough food to prevent the usual loss of weight It is definitely established that with a high caloric diet the mortality rate has been lowered and convalescence has been greatly shortened It is also believed that complications are less frequent than they were under former methods of treatment although relapses are perhaps slightly increased Carbohydrate being the food most easily digested should form a major portion of the diet Protein however is given in adequate amounts at least 1 Gm per kilo of body weight and fats are added in sufficient quantity to supply the caloric need The average patient with typhoid fever should receive from 3000 to 4000 calories per day depending in some measure upon his size and weight Since this diet must consist of liquids semisolids and soft foods it will be necessary to increase the carbohydrate beyond the usual intake of the average person Sugar must be used for this purpose and since milk sugar furnishes a sufficient caloric value without being too sweet it is used to increase the carbohydrate content of most diets Protein is given in the form of milk and eggs and curd Fats are supplied in butter and cream The chief articles of diet in typhoid fever are milk cream well cooked cereals such as rice grits cream of wheat strained oatmeal etc soft boiled

soft poached hard boiled or soft scrambled eggs toast or crackers fruit juices, stewed apples peaches or apricots apple float, butter, soups thickened with rice or barley flour creamed soups mashed or baked potatoes scraped meats or finely minced meat Simple desserts such as boiled custard, ice cream bread or tapioca pudding junket, cup custard blanc mange eggnog and jellies are allowed

From this list an ingenious nurse can prepare many combinations using various flavorings to keep the patient from tiring of any one food Lactose can be used in considerable amounts for sweetening The patient s food should be watched for its vitamin and mineral content Should the diet be low in either or both the deficiency should be corrected either by a rearrangement of the diet or supplying the deficiency from other sources When possible the patient should receive some foods which require mastication such as toast or crackers The type and quantity of food should be chosen for each individual patient No set formula should be followed other than to see that sufficient calories are taken One should never lose sight of the fact that one is treating a patient as well as a disease and due allowances must be made for the likes and dislikes of the individual

Hydrotherapy—The use of the cold tub bath as advocated by Brand has of late years been supplanted by sponge baths for the reduction of temperature and the improvement of the patient s well being A sponge bath correctly given is quite as efficacious as the tub In this type of hydrotherapy the patient is not moved from the bed A large rubber sheet is placed beneath him and by supporting the sides and ends of the rubber sheet it can be so designed as to form a shallow tub containing a sufficient amount of water to accomplish the necessary results A less extensive bath can be given in which the patient is sponged with water at a temperature of from 65° to 70° F Alcohol can be added to this if desired During the giving of any kind of bath friction of the patient s skin is of great importance in accomplishing the desired result The advantage of frequent bathing is that it quiets the nervous patient protects the skin reduces temperature and gives a sensation of well being and relaxation to the patient The baths should be given every four hours if the temperature is 102.2° F or over An ice cap to the head is usually most agreeable and ice caps to the abdomen are quite efficacious in reducing fever and in relieving a tendency to meteorism

Bowels—The ill effects of purgation in typhoid fever have long been known so that now no one would think of giving drugs to cause a daily evacuation At times mineral oil may be given if there is a tendency to fecal impaction Usually a daily enema of either normal salt solution or soap suds is quite sufficient

Treatment of Special Symptoms —*Toxemia*—For severe toxemia, fluids should be given very freely by mouth if possible, otherwise by hypodermoclysis Every typhoid patient should receive at least 3 liters of fluid within twenty four hours Hydrotherapy should be practiced regularly whether the temperature is high or not Headaches are usually controlled by the application of an ice bag or cold compresses Particular attention should be given to every patient who is delirious since in their delirium they may get out of bed or do themselves some injury

Tympanites and Diarrhea.—Meteorism like diarrhea is usually due to dietary indiscretions and can be controlled by further regulation of the food The majority of patients with marked distention are quite toxic Diarrhea in the majority of instances is due either to an excessive amount of fat in the diet or to the inability of the individual to digest properly the amount of food given The diarrhea can usually be controlled by eliminating fat and fruits from the diet and by administering bismuth subcarbonate in doses of 30 to 60 grains every three to four hours Opiates should not be given if they can be avoided

Hemorrhage—Hemorrhage from the bowel may vary considerably in amount The appearance of even a small amount of blood in the stool of a patient with typhoid fever is a warning for the physician to be on his guard All bleeding should be looked upon as a critical sign and should be so treated until proved otherwise In the event hemorrhage occurs all food by mouth should be stopped Small pieces of ice are given and

nished by typhoid vaccination conclude that a large proportion of immunized persons are protected for a period of two or three years after vaccination They also observed that, using the same method of determining immunity in persons previously immunized, the intracutaneous injection of 0 1 cc of typhoid vaccine produces an immunologic response equivalent to that obtained by the previous 3 subcutaneous injections The local and systemic reaction following the intracutaneous injection is relatively mild By employing this method or the subcutaneous injection of 0 5 cc of typhoid vaccine each year individual immunity can be kept at its height During an epidemic or in any household where typhoid fever develops, all exposed individuals should receive prophylactic inoculations

Treatment —In no disease is it more important to have the services of a skilled attendant or nurse than in typhoid fever Fortunately in the past twenty five years the profession has learned that good nursing care is of greater importance than drugs in the treatment of this disease If possible all patients with typhoid should be hospitalized When this is not feasible the patient should be placed in a clean well ventilated room, which has been stripped of its unnecessary furnishings and properly screened Should the services of a nurse not be available then some responsible member of the family should be given the necessary instructions concerning the care of the patient This should consist first and foremost in training and demonstrating how to disinfect thoroughly all excreta bedclothes dishes and anything else which might be contaminated All members of the family should be inoculated During the progress of the disease the nurse should be informed of the complications that may arise and should be instructed to report at once to the physician any unusual happening such as severe abdominal pain tarry or bloody stools, a sudden rise or sudden drop in fever or any marked change in the pulse rate

The patient should be in a bed which is properly protected by sheeting to prevent soiling and contamination of the mattress From the outset a regular regime should be instituted and followed Particular attention should be paid to the teeth and the mouth should be kept clean Purgatives of all kinds are to be avoided especially after the first week of the disease A daily bath is not only necessary but it affords ample opportunity for a careful inspection of the patient Alcohol rubs are of great value and can be given three or four times daily They are of assistance in keeping the skin in good condition As a rule visitors do much more harm than good If admitted they should be present for only a short time

Diet —In the past patients with typhoid fever have suffered greatly from undernutrition and avitaminosis because of the popular belief that typhoid patients should receive only certain types of food The diets formerly prescribed were extremely limited and poor in caloric value Since the demonstration by Coleman and Shaffer that a patient can go through typhoid fever without marked loss of weight the restrictions previously imposed have been removed and it is now possible to feed the typhoid patient enough food to prevent the usual loss of weight It is definitely established that with a high caloric diet the mortality rate has been lowered and convalescence has been greatly shortened It is also believed that complications are less frequent than they were under former methods of treatment although relapses are perhaps slightly increased Carbohydrate being the food most easily digested should form a major portion of the diet Protein however is given in adequate amounts at least 1 Gm per kilo of body weight and fats are added in sufficient quantity to supply the caloric need The average patient with typhoid fever should receive from 3000 to 4000 calories per day depending in some measure upon his size and weight Since this diet must consist of liquids semisolids and soft foods it will be necessary to increase the carbohydrate beyond the usual intake of the average person Sugar must be used for this purpose and since milk sugar furnishes a sufficient caloric value without being too sweet it is used to increase the carbohydrate content of most diets Protein is given in the form of milk and eggs and curd Fats are supplied in butter and cream The chief articles of diet in typhoid fever are milk cream well cooked cereals such as rice grits cream of wheat strained oatmeal etc soft boiled

a most perplexing problem The infection is usually in the gallbladder for which cholecystectomy has been performed The patient should be told of the existing condition taught how to take care of himself and not allowed to handle food for others

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PARATYPHOID FEVER

Definition—Paratyphoid fever is an acute generalized infection which closely resembles both clinically and pathologically infection with *Eberthella typhosa* It is caused by the paratyphoid bacillus A or B According to the new terminology paratyphoid bacillus A is now known as *Salmonella paratyphi* and paratyphoid bacillus B as *Salmonella schottmulleri*

Etiology—No marked differences have been discovered between infection with paratyphoid bacillus A and paratyphoid B Epidemics of typhoid and paratyphoid may exist at the same time with one predominating over the other as was observed in various localities during the World War Immunization with *E typhosa* does not protect against infection with either *S paratyphi* or *schottmulleri* Since the human body is believed to be the normal habitat of the *E typhosa* it is equally true that it is also the normal habitat of the *Salmonella* organisms The method of transmission is similar to that previously described under Typhoid Fever

Bacteriology—The *S paratyphi* and *schottmülleri* are intermediaries between the *E typhosa* and the colon bacilli In 1896 Achard and Bensaude first recognized and described *S schottmülleri* The organism was isolated from the blood in 1898 by Gwyn In 1903 Paladino Blandino isolated *S paratyphi* from water This organism is more closely related to the *E typhosa* than *S schottmülleri* the latter resembling *B enteritidis* which is a common cause of poisoning by spoiled meat

Cultural Qualities—Both organisms grow on ordinary culture media where they are distinguished with some difficulty from *E typhosa* On bismuth sulfite media the *Salmonella* group of organisms produces colonies with a greenish color in contrast to the black colonies of the *E typhosa* The *Salmonella* organisms ferment glucose levulose and maltose much more than does the *E typhosa S paratyphi* forms acid in milk whereas the *S schottmulleri* forms alkali Agglutination tests are usually necessary to distinguish them from the *E typhosa*

Morbid Anatomy—Pathologic findings in typhoid vary but little from those of paratyphoid fever As a general rule the intestinal lesions of paratyphoid fever are more in the nature of a superficial necrosis of the lymphoid structures than like the deep ulcerations of typhoid Hemorrhage and perforation are not so common

Symptoms—As a rule the incubation period is slightly shorter than that of typhoid and the onset is much more abrupt Frequently there is a chill and the headaches are more intense however upon clinical grounds it is impossible to differentiate these infections from ordinary typhoid fever This is made possible only by laboratory examinations Paratyphoid as a rule is a milder infection and of shorter duration diarrhea is usually present and there are frequent sweats Relapses and recrudescences are about as common as in typhoid The typical roseola seen in typhoid fever occurs in paratyphoid Sometimes the onset may be with nausea vomiting abdominal pain and marked diarrhea which is frequently mistaken for food poisoning Occasionally one or more joints are involved in this infection a picture resembling that of acute rheumatic fever

Complications—These are similar to the ones previously pointed out as occurring in

the lips are moistened frequently with a mixture of lemon juice glycerin and water Absolute quiet is necessary An ice cap is placed on the abdomen with sufficient protection to prevent the skin from becoming too cold It is customary to give by hypodermic 100 units of parathyroid extract since this is of value in helping to increase the coagulability of the blood Calcium gluconate in 1 Gm doses intravenously is thought to be of value Morphine should be withheld unless there is marked restlessness anxiety and evidence of peripheral vascular collapse Transfusions of salt solution with glucose or whole blood should be given if indicated It is commonly believed that giving large quantities of fluid increases the tendency to hemorrhage by increasing the blood pressure but observation has not confirmed this suspicion Food is usually withheld for at least twenty four hours or until all evidence of bleeding has ceased

Perforation—The only treatment of any value for this condition is immediate surgical intervention Delay increases the mortality and robs the patient of his only chance of recovery It is much better to have an exploratory operation on a doubtful diagnosis than to wait too long for positive symptoms to appear Under the most favorable conditions the mortality is unusually high—50 to 60 per cent

Cholecystitis seldom requires surgical intervention Usually local applications of either hot or cold packs can be used to tide over an attack however the patient should be carefully watched and with increase in pain and a rising leukocyte count operation is indicated

Heart Failure—The use of sponge baths and an increased fluid intake have done much to prevent the development of myocardial weakness in typhoid fever A patient with this disease should be kept absolutely quiet with medication according to his needs

Phlebitis occasionally occurs The extremity involved should be kept warm at rest and elevated Sometimes the application of an ice bag over the involved vein affords comfort

Bed sores should not occur in this disease They usually result from inadequate attention Should they appear the patient should be put on a rubber ring turned on his side all pressure removed and healing applications applied

Drugs—In typhoid fever very few drugs are of any value In treating some of the complications they may be of definite value. Treatment of bacilluria with hexamethylenamine mandelic acid or with sulfanilamide is of value The use of various sulfonamide drugs in the treatment of typhoid fever has been very disappointing Seemingly it has no beneficial action on the progress of the disease although it is of value in treating the cystitis which accompanies the infection Ill effects may follow the administration of these remedies particularly the effect on the blood forming organs Codeine for headaches mineral oil for constipation phenobarbital for restlessness are all useful

Vaccine and Serum Treatment—The treatment of typhoid fever with typhoid vaccine has been tried by many observers but results from a large series of cases have not substantiated the claims for this form of therapy When given at all the dosage must be quite small in comparison with the doses used for the prevention of the disease The remedy has been administered both subcutaneously and intravenously The initial intravenous dose should not be over 10 000 000 organisms the subcutaneous dose less than 500 000 000 Between injections there should be an interval of several days Recent reports concerning the use of an antitoxic serum made by immunizing horses to the toxin of the typhoid bacillus indicate that it has been satisfactory from the standpoint of an immunologic experiment but so far the results do not justify the assumption that this will be a popular method of combating the disease The administration of typhoid vaccine to chronic carriers has appeared to be of little avail

Treatment of Convalescents—After the temperature of a patient has been normal for a week or ten days he is allowed to be propped up in bed and after three or four more days he is allowed to be out of bed then as his strength returns he begins very slowly with a moderate amount of exercise The diet is gradually increased during convalescence until after the first ten days it has reached its normal level Strict attention should be given to the discovery of possible carriers The treatment of carriers presents

convulsions (in children), cough pneumonia, splenomegaly, or muscle weakness may appear The course is brief usually two to five days and the mortality very low Generally there is leukopenia and cultures from the stool occasionally from the urine and rarely from the blood may be positive for *S suipestifer* Specific agglutinins appear during convalescence

Sporadic cases usually begin with an acute onset of high fever occasionally preceded by a chill In a few cases the onset is more gradual In about two thirds of these cases the bacteremia is uncomplicated by the development of focal lesions and the course

the organisms have been isolated from the sputum or from the lung at autopsy

Bone and particularly joint lesions occur in about 20 per cent of cases according to Harvey The lesion is usually a pyarthrosis with organisms present in the greenish fluid which accumulates in the joint space and with involvement of the adjacent bone Any joint may be involved and the lesions frequently occur after the acute systemic infection has subsided

Purulent meningitis particularly in children bacterial endocarditis superimposed on damaged valves pyelonephritis and abscesses in various parts of the body have

Fig 21 —Clinical course of *S suipestifer* infection in a twenty-one-year-old primiparous woman who had had a spontaneous delivery during the disease and who developed both pneumonia and arthritis of the sacroiliac joint The baby appeared ill for the first week but recovered *S suipestifer* was isolated from its stools on the twentieth day of life

is that of a typhoid like febrile disease with leukopenia and fever lasting one to three weeks Tachycardia is much more common than bradycardia and although cough coryza headache delirium stupor vomiting constipation and diarrhea all may occur as in typhoid fever they are much less frequent symptoms Intestinal hemorrhages and perforation have not been described

Focal complications are more frequently observed than in typhoid and paratyphoid fever Pulmonary lesions particularly bronchopneumonia have been noted in about one third of the cases Lobar pneumonia pleural effusion empyema and pericardial effusion have been observed In some cases

all been described as complications of *S suipestifer* infection

The characteristic laboratory findings are a mild anemia which progresses during the disease and leukopenia which may be followed by the development of a leukocytosis when focal complications appear Bacteremia occurs in a very high percentage of cases and persists throughout most of the febrile course The agglutination reaction becomes positive to a high titer in most cases Positive urine cultures are frequently obtained but positive stool cultures are rare

Diagnosis —The diagnosis of *suipestifer* infection is usually easy if the disease is kept in mind and blood cultures are taken

typhoid fever Quite a number of authors consider the frequency of respiratory complications as evidence of infection with the *Salmonella* organism

Diagnosis—Practically all authorities are of the opinion that paratyphoid fever cannot be differentiated clinically from typhoid without laboratory aid At present, agglutination tests and recovery of the organism from the blood stream are the methods of greatest importance for recognition of the disease

Prognosis—Prognosis is influenced by the same considerations pointed out in typhoid fever However the mortality rate is lower than that of typhoid fever

Treatment—Treatment does not differ in any way from that previously outlined for typhoid

JAMES E PAULLIN

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SALMONELLA SUIPESTIFER INFECTION

Definition—*Salmonella suipestifer* infection is an acute illness due to organisms of the hog cholera bacillus group It may occur in epidemics as a gastro enteritis or sporadically as a form of paratyphoid fever which is characterized by a tendency to affect children or debilitated individuals by the absence of intestinal lesions and by the frequency with which bacteremia pulmonary lesions and joint involvement occur

History—Although *Salmonella suipestifer* (hog cholera bacillus) was first isolated in 1885 by Salmon and Smith from swine it was not until 1902 that infection in man was described when Longcope reported two cases of fever due to a paracolon bacillus later identified by TenBroeck as a member of the hog cholera group With the interest in enteric disease occasioned by the World War these organisms were identified as the causative agents of paratyphoid occurring in Mesopotamia among troops who had been vaccinated with TAB vaccine In recent years an increasing number of gastro-intestinal outbreaks and sporadic cases have been reported from various parts of the world

Etiology—*Bacteriology*—There are three members of the Paratyphoid C group which have been isolated from cases of this type. These are indistinguishable from *S schottmulleri* (Paratyphoid B bacillus) by the ordinary fermentation tests, but can be distinguished by their action on special sugars and by their serologic reactions in properly prepared antisera

The three species are

S hirschfeldii (Paratyphoid C bacillus Eastern type of *S suipestifer*) ferments arabinose and trehalose antigenic formula VI VII c 1 4 5

S cholerae suis (hog cholera bacillus American type of *S suipestifer*) does not ferment arabinose and trehalose does not produce H_2S antigenic formula VI VII c 1 3 4 5

S cholerae suis var kunzendorf (European type of *S suipestifer*) does not ferment arabinose and trehalose produces H_2S antigenic formula VI, VII— 1 3 4 5

Epidemiology—The source of *suipestifer* infection in man is usually hard to identify Certain epidemic outbreaks have been traced to infected meat shellfish, ice cream and other foods prepared under poor sanitary conditions and in some cases obviously contaminated with hog wastes However although the two varieties of *S cholerae suis* are natural pathogens of swine it has not been possible to trace most human infections to contact with these animals

Incidence—Susceptibility to *suipestifer* infection seems to be universal in man but the infectiousness is less marked than with the Paratyphoid A and B bacilli Thus although cases have been reported at all ages in all races the majority have occurred in children or else in adults debilitated by other diseases surgical operations or malnutrition

Morbid Anatomy—There are no specific pathologic lesions in *suipestifer* infection The findings are characteristic of any generalized infection—namely acute splenic tumor focal necrosis of the liver cloudy swelling of the kidneys and widespread petechial hemorrhages The absence of intestinal lesions has been conspicuous

Symptoms—Epidemics of food poisoning due to *S suipestifer* occur among groups who have ingested heavily contaminated food After an incubation period of six to forty eight hours there is an abrupt onset of fever headache abdominal pains nausea vomiting and diarrhea In a few cases chills

often arises as a complication of diarrheal disease when the enteric organisms seem to gain more ready access to the lymphatics and blood stream and is frequently seen in elderly patients with constipation Trauma to the urinary passages as from an inlying catheter stasis in the bladder or obstruction to the ureters predispose to infection Thus pyelonephritis in childhood is often the result of congenital anomalies of the urinary tract, in later life prostatic hypertrophy in men and pregnancy or pelvic disease in women may obstruct the flow of urine Infection may be of the ascending type when there is obstruction to the bladder outflow but usually it reaches the kidney directly by lymphatics from the colon or by the blood stream It is probable that benign bacilluria occurs frequently and causes trouble only when the added factor of obstruction leads to stasis Urinary tract infections may be caused by any of the coliform bacilli in pure or mixed culture but the majority are due to *B coli* often in combination with the *Enterococcus* (*Strep faecalis*)

Although transient bacteremia with these organisms is not uncommon during the acute phase of pyelonephritis generalized infection and persistent bacteremia are rare except in infants and debilitated elderly patients

Morbid Anatomy—Acute infection with these organisms produces purulent inflammation In cases of bacteremia in infants there is a tendency to localization in the kidneys meninges lungs and serous cavities In surgical infections pus produced by the colon group has a greenish color and characteristic fecal odor The presence of *B pyocyaneus* imparts a bluish tint to pus

Contrary to earlier opinion the lesion in pyelitis has been found to involve the renal parenchyma as well as the pelvis and ureters and so the term pyelonephritis has come into common use for this condition In the acute phase the kidneys are swollen and the capsule strips with ease revealing small yellowish raised areas on a reddish surface On section there are yellowish streaks through the cortex dilatation and redness of the pelvis and ureters Histologically acute inflammation of the mucosa of pelvis and ureters is observed with leukocytes in the collecting tubules and minute abscesses or collections of inflammatory cells in the interstitial tissue In diabetic patients with pyelonephritis gangrenous changes involving the pelvis and papillae have been described In chronic cases the kidneys become contracted as a result of scarring and secondary proliferative lesions of the blood vessels are found

Pathologic Physiology and Chemistry—All the gram negative enteric bacilli possess potent endotoxins Consequently invasion of the blood stream by these organisms is associated with the same symptoms as those which follow the intravenous injection of typhoid vaccine chills fever headache and nausea Since *Proteus* produces large amounts of ammonia from urea urinary infections due to this organism are characterized by an extremely alkaline urine and a high incidence of calculi containing calcium phosphate calcium carbonate, or magnesium ammonium phosphate

The importance of infections of the kidney lies in their tendency to become chronic and thus to produce slow and progressive renal damage In some cases severe arterial hypertension develops perhaps because the proliferative arterial lesions in the involved area produce ischemia in uninvolved portions of the kidney as suggested by Weiss and Parker

Symptoms—The symptoms of colon bacillus infection are of two types local and constitutional The *local symptoms* are determined by the particular organ infected—gallbladder bile ducts appendix urinary bladder kidney—more than by the organism concerned and detailed descriptions of these conditions will be found in appropriate sections of this book The *constitutional symptoms* are most marked in cases of peritonitis suppurative pylephlebitis cholangitis or acute pyelonephritis In these patients severe shaking chills followed by episodes of high fever malaise and nausea are the rule Where there are purulent foci leukocytosis with a predominance of polymorphonuclear cells is marked and anemia develops rapidly

The incidence of urinary tract infection is considerably higher in women than men and diabetics are particularly subject to the disease In men some obvious mechanical

in obscure cases It should be suspected whenever a typhoid like illness occurs in which pneumonia pleural effusion, or joint lesions are observed It may occur even though the patient has been vaccinated with standard typhoid paratyphoid vaccine Diagnosis is usually made by the finding of a positive blood culture or the demonstration of the development of specific agglutinins during the course of the disease

Prognosis —Prognosis depends mainly upon the condition of the patient In 1400 epidemic cases the mortality has been reported as about 0 4 per cent In sporadic cases, the fatality rate is low in children and the disease mild whereas in infants and adults over 30 the death rate is high In the presence of pneumonia the mortality among reported cases has been about 40 per cent while cases with meningitis or bacterial endocarditis have been almost uniformly fatal

Treatment —No specific treatment of this infection is known at present A three day trial of therapy with large doses of 6 to 9 Gm (grains 90 to 135) daily of sulfathiazole or sulfadiazine is justified but these drugs have not proved efficacious in most cases of typhoid and paratyphoid fever General supportive measures and surgical treatment of any purulent foci which may serve to disseminate the infection are all that can be recommended

Prophylaxis —Since paratyphoid C infections occur in individuals vaccinated with standard typhoid paratyphoid vaccine, the inclusion of *S suipestifer* in such vaccines seems indicated This is particularly important in military medicine for troops are apt to be heavily exposed to enteric infections and to be debilitated by fatigue exposure disease and wounds That protective vaccination is effective was apparently demonstrated by Hirschfeld in the last war

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INFECTIONS WITH THE COLON GROUP OF ORGANISMS

Definition —The various forms of infection caused by the gram negative aerobic bacilli normally present in the intestinal tract may be considered together under this heading

Bacteriology —The colon bacilli include a number of organisms which can be isolated from normal stools The chief members of this group which are distinguished from the enteric pathogens by their ability to ferment lactose are *Aerobacter aerogenes* (*B lactis aerogenes*) *Escherichia coli* (*B coli*) and the *Paracolon bacilli* In addition two other gram negative bacilli, *Proteus* and *Pseudomonas aeruginosa* (*B pyocyaneus*) are found in feces and are apt to produce similar types of infection

Etiology —Since organisms of the colon group are normal inhabitants of the intestines it is only under special conditions that they gain access to the body cavities or tissue spaces where they may initiate infection

In the abdominal cavity surgical infections arise either as a result of actual perforation or of damage to the tissues of the bowel wall In appendicitis cholecystitis cholangitis and diverticulitis it is probable that obstruction by calculi or fecaliths is frequently responsible for the local changes which make the tissues vulnerable to infection Puerperal infections due to colon bacilli may occur as a consequence of poor obstetrical technique or of difficult labor Open wounds may become secondarily infected with gram negative bacilli particularly *Proteus* or *Pyocyaneus*

The most common disease produced by colon bacilli is urinary tract infection It

Management of urinary tract infections should include the following

1 Study of the renal function intravenous urography and if necessary cystoscopy and retrograde pyelography to evaluate the anatomical situation

2 Relief of obstruction if possible and care of disease of the large bowel

3 Forcing of fluids to maintain a free flow of urine thus washing out pus and cellular debris, whenever this is compatible with chemotherapy

4 Adequate chemotherapy to relieve acute symptoms and cure the infection if possible

5 Careful follow up study in order to recognize and treat recurrences promptly

Chemotherapy offers several possibilities MANDELIC ACID which is effective only if the urine pH is below 5.5 is taken in doses of 3 Gm (45 grains) four times a day Ammonium mandelate is usually used since it will acidify the urine itself This drug is useful in patients who cannot tolerate the sulfonamides but may cause acidosis in patients with poor renal function or *Proteus* infections in whom the urine is apt to remain alkaline Fluids should be restricted to give a daily output of approximately 1000 cc

The SULFONAMIDES are the most effective drugs for the treatment of urinary tract infections Sulfathiazole is the drug of choice because it is effective with a high fluid intake in doses of 0.5 Gm (7½ grains) four times a day in the average adult unless the infection is very severe or caused by *Proteus Pyocyaneus* or *Streptococcus faecalis* when 1 Gm (15 grains) every four hours may be necessary The dose should be scaled down proportionately in a patient with diminished renal function Enough sodium bicarbonate to render the urine slightly alkaline will not inhibit the drug and frequently will relieve dysuria and frequency It is important to emphasize the fact that chemotherapy is relatively ineffectual without an attack on the predisposing cause Thus surgical treatment of such lesions as calculi and prostatic hypertrophy is essential and in the benign infections of older patients attention must be given to improvement of the function of the large bowel

Prophylaxis—Since the organisms of the colon group are not particularly virulent except under abnormal conditions which enable them to gain access to the tissues no specific preventive measures are necessary The prevention of serious infections of this type consists mainly in the prompt recognition and treatment of abdominal disease such as appendicitis and cholecystitis the proper handling of labor and scrupulous cleanliness in the handling of open wounds Above all it is important to consider infections of the urinary tract as potentially serious since they are prone to recur and to produce renal damage and even severe hypertension in some cases

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BACILLARY DYSENTERY

Definition—Bacillary dysentery is an infectious disease caused by *Bacillus dysenteriae* It is characterized pathologically by inflammation of the colon clinically by abdominal pain and tenesmus and the frequent passage of stools containing mucus pus and blood

History—Hippocrates applied the name diarrhea to the frequent passage of liquid stools and dysentery to the passage of bloody stools Galen and other ancients gave the term its present connotation by making it include tenesmus and the passage of stools containing mucus The disease can be traced in various historic epidemics especially in wars

difficulty such as neurologic bladder, prostatic hypertrophy, urethral stricture or calculus can usually be found to account for the infection

Acute pyelonephritis may be preceded by a prodromal period of several days when malaise, slight fever, dysuria, urgency and frequency are the only symptoms, or it may begin abruptly Renal infection is usually ushered in with a shaking chill followed by fever which may reach 105° F or more in severe cases Headache nausea anorexia and vomiting are common symptoms Most patients complain of pain in the back or flank and burning on urination Examination usually reveals tenderness in the costovertebral angle and enlargement of the kidney Localizing signs may be lacking at first particularly in children In some cases the onset is not abrupt but insidious and the disease may remain chronic and unrecognized for years

The course of most attacks of acute pyelonephritis is benign The symptoms usually *disappear in one to two weeks but infection* is apt to persist longer Patients successfully treated with the sulfonamides should recover in a few days but must be watched for recurrence after the cessation of chemotherapy

The *laboratory findings* include polymorphonuclear leukocytosis mild secondary anemia and pyuria The urine is cloudy with small amounts of albumin and many white blood cells The bacilli can usually be seen in the sediment Casts are rarely found and red blood cells appear only in very acute *cases or in patients with calculus* or hemorrhagic cystitis The blood chemistry is not altered except in chronic cases with renal damage Culture of the urine yields an abundant growth of the infecting organism and blood culture is frequently positive in the early stage of an acute attack

Diagnosis —Colon bacillus infection may be suspected from the odor and color of the pus if any is found and from the character of the constitutional reaction but the diagnosis can only be established by bacteriologic *methods* Blood culture should be performed in cases with high fever and a fresh specimen of urine examined and cultured in all cases of suspected urinary tract infection In women, the urine must be obtained by catheter in order to be certain that extraneous organisms are excluded

Acute pyelonephritis does not often present a problem in diagnosis but occasionally tenderness over the ureters may suggest appendicitis or pelvic inflammation Severe cases with chills fever, leukocytosis pain in the side and consequent limitation of motion of the diaphragm may be confused with pneumonia A few patients may have high fever, little local *pain or tenderness relative* bradycardia, and only slight leukocytosis giving a picture difficult to distinguish from typhoid fever a disease in which pyuria is often observed

Prognosis —In severe infections due to the colon group prognosis depends on several factors First pure colon bacillus infections have a better prognosis than mixed infections particularly in the abdomen where the presence of pyogenic cocci and anaerobic bacilli adds greatly to the severity of the disease Second the age and condition *of the* patient make *a tremendous difference* infants and elderly patients do badly Third, the type of anatomic difficulty which gave rise to the infection has a marked bearing on prognosis

In the urinary tract the degree of destruction of the renal parenchyma and the possibility of remedying the obstruction to urinary flow will influence the outcome of the acute attack and the ultimate course of the disease Urinary infections in diabetic patients and infections due to *Proteus* or *Pyocyaneus* are apt to be resistant to therapy

Treatment —The treatment of these infections should be of two types—first general supportive measures and second therapy of the local infection In the case of intra abdominal infection surgical intervention is usually necessary The sulfonamides should be given parenterally or by mouth in large doses of 1 to 1 5 Gm (15 to 22 grains) every four hours after an initial dose of 4 Gm (60 grains) in severe colon bacillus infections such as cholangitis but in the face of suppuration improvement will be slow Sulfathiazole is the most potent drug against organisms of the colon group although sulfadiazine is also effective and is better tolerated by many patients

Symptoms —Dysentery has been symptomatically classified into the following groups by Manson Bahr (1) mild (2) acute (3) fulminating (4) relapsing and (5) chronic The fulminating group may be divided into two subgroups—the choleraic and the gangrenous The symptoms of dysentery vary considerably with the severity of the disease

Mild dysentery may be merely a diarrhea although the stools usually contain mucus

The severity of *acute dysentery* varies greatly The *incubation period* is from twelve hours to seven days The *onset* is sudden with griping pain in the abdomen followed shortly by diarrhea The symptoms increase in severity and frequency and mucus appears early in the stools Within twenty four or forty-eight hours the patient passes typical dysenteric stools consisting of mucus pus and blood from five to ten times a day or much more frequently There is straining or tenesmus on account of the severe rectal irritation The temperature rises to 38° C or over There may be headache vomiting and signs of toxemia malaise or drowsiness The abdomen is tender over the colon The onset may simulate acute appendicitis operation has been performed as a result of this mistake in diagnosis

In addition to enteric symptoms a considerable proportion of cases in America are reported as showing at the outset symptoms not usually associated with dysentery Meningitic pneumonic and agranulocytic forms occur These forms described by Felsen are ascribed by him to adaptations of the disease to a new environment and virgin soil They are rarely seen in countries where dysentery is common

The *stools* in bacillary dysentery are so characteristic that a diagnosis can practically always be made directly from them a matter of great importance in the early institution of treatment

The typical stool consists of mucopus which varies in color from pale pink to bright red according to the proportion of blood The microscopic picture is different from that of any other disease and is found even in the early liquid fecal stools A coverslip preparation of a tiny fragment well mixed with saline shows an abundant cellular exudate very rich in polymorphonuclear leukocytes variable quantities of red blood cells and always a certain proportion of large cells some of which are large mononuclears while others are macrophages or clasmatocytes The last are specially important because not only are they characteristic of bacillary dysentery but being very large and often containing ingested red blood cells they are frequently mistaken for dead amebae A notable characteristic of the exudate is that the pus cells are undergoing toxic necrosis the nuclei become pyknotic and finally disappear leaving the so-called "ghost cell

Sigmoidoscopy shows the mucous membrane intensely hyperemic with grayish superficial necrosis edema is very evident and there is a profuse moist mucous exudate Positive cultures are readily obtained by swab from the mucosal surface

The *blood count* may be normal or show a moderate leukocytosis rarely above 10 000 The average counts in ninety uncomplicated cases were Shiga dysentery 12 338 mannite fermenting group 10 063 (Peking Union Medical College Hospital Series) The leukocytic picture as described by Blatt and Shaw shows a wide variation counts varied from 8000 to 20 000 averaging about 13 000 Extreme toxicity is associated with leukopenia of from 2500 to 6500 There may be an almost complete disappearance of granulocytes such cases always ending fatally *Agglutinins* appear in the blood serum usually from the sixth to the tenth day and consequently serodiagnosis is of value only in the later stages of the disease

The *fulminating forms* of dysentery are marked by a very acute onset and severe toxemic symptoms The *choleraic type* with vomiting and great loss of fluid absorption of toxins and collapse may be mistaken for cholera The diagnosis is made from the passage of mucus with or without blood from which the cholera vibrio is absent The *gangrenous form* also begins suddenly with headache vomiting pyrexia and other symptoms of severe toxemia The abdominal pain and tenesmus are very great but later may disappear as the toxemia increases The stools in the last stages are free from mucus owing to complete necrosis of the mucous membrane

Mild recurrent dysentery is manifested by a recurrent diarrhea and the passage of a little mucus and blood which persists when treatment is inadequate in the first attack

Chronic Bacillary Dysentery —Dysentery lasting for over one month is considered chronic The persistence usually results from

The bacteriology of dysentery was conclusively established by Shiga (1898) Kruse (1900) and Flexner (1900) The disease which was one of the most important of the 1914–1918 War first broke out in Gallipoli in 1915 and was responsible for a high proportion of the 120 000 casualties from sickness in that area

Incidence—Bacillary dysentery occurs throughout the world and is everywhere commoner than the amebic form Although predominantly a disease of the tropics it is more prevalent in America and Europe than was formerly supposed Felsen states that the incidence in the United States in 1937 was approximately sixteen times that reported for *1933* and that as reported cases of bacillary dysentery increase the cases of unclassified diarrhea enteritis and dysentery ' rapidly decline

Etiology—The most important factors in transmission are flies crowding unsanitary disposal of feces and food contamination especially uncooked vegetables and fruit also direct contagion, *e g* in hospitals asylums homes, and other places

Bacteriology— The bacilli credited with the causation of dysentery all belong to a natural genus which presents the following characters They are short rods destitute of flagella and nonmotile, forming no spores *not liquefying gelatin negative to Gram s* stain and fermenting glucose and sometimes other sugars and alcohols without the formation of gas (Andrewes and Inman) Four groups of dysentery bacilli are generally accepted as definitely pathogenic Shiga Flexner Sonne and Schmitz

In cultures B dysenteriae Shiga and Schmitz do not ferment mannite the other groups are mannite-fermenters

B dysenteriae Flexner constitutes a group of bacilli which can be distinguished by agglutination Five races were thus distinguished by Andrewes and Inman (1919) and named V W X Y Z Since then an exhaustive study in India by J S K Boyd ha led to a modification of this *classification and to recognition of* six races of *B dysenteriae* Flexner with a group antigen and type antigens specific to each and in addition three races named *B dysenteriae* Boyd which have Flexner biochemical reactions but no group antigen Boyd s article (1940) should be referred to for details of this complex subject

Shiga (1933) recognizes (1) *B dysenteriae* (Shiga Kruse) (2) *B metadysenteriae* (including Schmitz bacillus and the Flexner group (3) *B paradysenteriae* (Sonne)

The Shiga bacillus generally causes more severe symptoms than the others though Flexner may produce very severe dysentery The Sonne bacillus has given rise to numerous epidemics of a comparatively mild dysentery or in some cases to symptoms similar to those of *Salmonella* 'food poisoning' Shiga bacillus produces a neurotropic exotoxin as well as an enterotropic endotoxin the other groups only an endotoxin

Morbid Anatomy—The toxin of *B dysenteriae* causes acute inflammation of the whole length of the colon and the termination of the ileum, leading to coagulation necrosis of the mucosa and ulceration In chronic dysentery the distal part of the colon is affected more often and more severely than the proximal The earliest lesions are in the lymphoid follicles of the colon (Manson Bahr) which before long stand out like distinct grains of sand on a red background of inflamed mucosa (Felsen) Coagulation necrosis of the mucous layer supervenes Microscopically this is seen as a thick necrotic layer densely packed with polymorphonuclear leukocytes at the base of which are remnants of Lieberkühn s follicles The submucosa is edematous and the capillaries in it may contain macrophage cells Separation of the necrotic membrane leaves ulcers with irregular margins or in severe cases extensive raw surfaces Necrosis as a rule is superficial to the muscularis mucosae but it may go deeper in places and exceptionally may perforate the serosa

Chronic dysentery causes numerous ulcers in a thickened fibrosed mucous membrane

In healing the mucous membrane regenerates from the remnants of Lieberkuhn s *follicles but when necrosis and exfoliation* have been extensive or in chronic fibrosis severe scarring and narrowing of the lumen may ensue Mucous glands may be nipped off in scar tissue and form cysts

Bacillus dysenteriae rarely invades the blood stream though *occasional cases* have been reported

The changes *in other organs* are usually slight Parenchymatous degeneration of the myocardium is sometimes found (Blatt and Shaw) The adrenals may show degeneration of or hemorrhages into the medulla The brain is found to be slightly edematous and shows degenerative changes of the ganglion cells in cases affected by the dysenteric neurotoxin

isolation in treating patients are important factors in prevention In endemic regions vegetables and fruit should be sterilized

Vaccines—Vaccines made in the ordinary way may cause severe local or general reactions especially in the case of the Shiga bacillus Vaccines treated with immune sera or detoxicated by formalin have been recommended Besredka introduced the method of oral administration of killed dysentery bacilli Reports of the results obtained by various methods are conflicting Kauntze inoculated 50 000 East African porters without improving the death rate from dysentery Gautier (1024) however got apparently good results in a mixed Shiga Flexner epidemic by means of orally administered polyvalent vaccine and Iguchi and others (1032) using an oral vaccine on 130 000 school children during two successive years reduced the morbidity rate of dysentery by half

Treatment—Complete rest in bed is highly important Castor oil 15 cc (½ ounce) may be given early to evacuate indigestible bowel contents

Diet must be such as will leave a minimum of residue in the bowel In the early acute stage fluid intake should be as large as possible and may be given as saline or clear soup to replace loss of salt Nourishment is restricted to albumen water orange juice or cabbage water tea with lactose arrowroot or rice water Milk is unsuitable at this stage With improvement milk fruit juices and smooth cereals can be added and still later further additions should gradually be made of eggs crackers and butter custards milk puddings toast fish chicken and mashed potatoes Return to normal diet should always be gradual and full diet should not be allowed till healing is complete this is shown by complete disappearance of mucus from the feces and of leukocytes from the microscopic specimen

A breast fed infant should continue with breast feeding An artificially fed infant does well on lactic acid milk In either case milk should be stopped if the child is vomiting and normal saline given by mouth instead

Chemotherapy—The treatment of bacillary dysentery has been revolutionized by the introduction of some of the newer sulfonamide derivatives Almost uniformly favorable clinical results have followed the use of sulfaguanidine in this infection The initial dose of sulfaguanidine as recommended by Marshall is 0 1 Gm per kilogram of body weight while the maintenance dose is 0 05 Gm per kilogram of body weight every four hours until the stools are reduced to less than five in twenty four hours With the great majority of cases 5 to 6 days of treatment is sufficient Sulfaguanidine appears to be effective against all the various strains of dysentery bacilli Its most striking effect however, is against the Flexner and Shiga strains

The only objections to sulfaguanidine are that it is absorbed into the bloodstream to such an extent that it gives rise to frequent and sometimes severe reactions It is also ineffective in the presence of ulcerating lesions of the bowel

More recently succinylsulfathiazole has been introduced because of its minimal absorption from the intestinal tract When administered to patients the drug produces a profound change in the physical characteristics and the bacterial flora of the feces The stools become small in bulk semifluid and relatively odorless and the number of colon bacilli is markedly reduced Succinylsulfathiazole is only slightly absorbed from the intestinal tract producing blood levels of 0 6 to 1 0 mg per 100 cc

Smythe and his co workers found that succinylsulfathiazole was just as effective as sulfaguanidine without its potential toxic effects and therefore believe succinylsulfathiazole to be the drug of choice in the treatment of bacillary dysentery The dosage recommended is 0.25 Gm per kilogram of body weight initially followed by 0 04 Gm per kilogram of body weight every four hours for at least six consecutive days On this program 85 per cent of the patients treated were quickly cured Smythe stresses the importance of repeated stool cultures for at least three weeks after drug treatment has been discontinued From the evidence so far available it would appear that succinylsulfathiazole is just as effective as sulfaguanidine and probably less toxic If further investigation bears out preliminary observations it may prove to be the drug of choice

inadequate treatment in the acute stage or too early return to a normal diet and activity The patient constantly passes loose stools containing small amounts of mucus The condition may last for years and end in death from exhaustion or may slowly disappear Sigmoidoscopy shows the mucosa diffusely red and granular Generally there are numerous shallow ulcers Small ulcers on top of swollen papules are sometimes seen The bowel wall is thickened Sessile papillomata and polypi are occasionally found Cultures of dysentery bacilli have been obtained by the writer from swabs made directly from the ulcers in a large proportion of such cases

Bacillary Dysentery in Infants—It was first demonstrated by Duval and Basset that the bloody diarrhea of infants was due to *B dysenteriae* and this observation has been amply confirmed by Flexner and Holt and subsequently by many others The disease occurs in breast fed as well as in other infants (26 out of 237 cases in Holt s series), may be mild or severe and causes constitutional symptoms which are not always proportional to the degree of local inflammation as judged by the discharges According to Davison persistent passage of bloody stools or of stools containing much pus is practically always evidence of dysentery infection which can be demonstrated by culture or serum agglutination

Toxemia and dehydration are more severe in children than in adults The onset may be marked by vomiting or convulsions and the patient is drowsy apathetic and difficult to feed the temperature may be high and loss of weight rapid Death usually occurs in the acute stages but may result from marasmus after dysentery has disappeared

Complications—*Arthritis* mono or poly articular occurs usually in Shiga infections after the acute stage is past Other complications are bronchopneumonia in children toxic myocarditis, neuritis conjunctivitis and iridocyclitis Sequelae are anemia or edema due to malnutrition and stenosis of the colon

Diagnosis—Diagnosis of bacillary dysentery can be made from the cellular exudate seen through the microscope This should be confirmed by culture

The diseases from which bacillary dysentery has to be differentiated are amebic dysentery, balantidial dysentery schistosomiasis, malarial 'dysentery, cholera intussusception, mucous colitis ulcerative colitis tuberculous ulceration of the colon, and carcinoma Of these amebic dysentery is the commonest cause of error, but it can be distinguished by examination of the stools In a typical case of amebic dysentery the stool is liquid and reddish brown, containing shreds of mucus Under the microscope it shows comparatively few leukocytes with a preponderance of mononuclears over polymorphonuclears The leukocytes do not show signs of toxic necrosis and autolysis but are eroded from their periphery by proteolytic digestion, the nucleus disappearing last Charcot Leyden crystals are often present. Finally the diagnosis is made by finding motile *Entamoeba histolytica* containing red blood cells The commonest error is to mistake macrophages in a bacillary stool for dead amebae, and a motile *E coli* or other nonpathogenic ameba may also lead one astray *E histolytica* may be found in a bacillary exudate in a mixed infection The cellular exudate in bacillary dysentery being much more profuse than in amebic it dominates the picture

The onset may closely simulate acute appendicitis Features pointing to a diagnosis of dysentery are shift of pain and tenderness with change in the position of the body and a low leukocyte count After twelve to twenty four hours characteristic dysentery will have set in

Serum agglutination is diagnostic in chronic Shiga infections if the titer is above 1 40 it is less reliable in Flexner cases

Prognosis—Mortality varies enormously It is much higher in children than in adults In Blatt and Shaw s series of 356 children the mortality was 17 per cent During the war it did not exceed 2 7 per cent in Macedonia Egypt and Mesopotamia among the British Forces from 1915 onward The invalidism caused by the disease is considerable Although in 50 per cent of a series of typical cases diarrhea lasted only eight days the average number of days of treatment for the 2000 cases in the British Army during 1917 and 1918 was 141

Prophylaxis—Sanitary disposal of feces fly prevention food protection and strict

may be applied directly to the ulcers by means of a cotton swab

The diet in chronic cases must be bland but nourishing and when a long continued diet is prescribed it must contain sufficient protein and the essential vitamins

Autogenous vaccines are sometimes effective in chronic cases The initial dose of Flexner vaccine may be 10 000 000 bacilli subsequent doses every four to seven days may be increased up to 100 000 000 Shiga vaccine must be given cautiously commencing with not more than 5 000 000 and increasing to a maximum of 15 000 000

Surgical intervention is necessary if ulceration of the colon is present higher up than can be reached by the antiseptic solution or in the very severe cases where complete rest of the colon is indicated The first can be inferred when the patient can retain only small quantities of the solution and when cultures taken on swabs from the sigmoid continue to yield dysentery bacilli even when the visible length of bowel is improving For this condition appendicostomy is the operation of choice the upper end of the colon can thus be reached with Dakin s solution If the aim is to set the bowel completely at rest cecostomy or ileostomy may be performed The latter is most effective in that while all fecal matter is diverted from the diseased bowel the patient can be given an abundant nourishing diet and the colon irrigated with Dakin s solution through the lower ileostomy opening When the dysentery is cured continuity of the bowel can be restored by operation

Treatment of Carriers —Kirby and Rantz have shown that carriers of dysentery bacilli can be treated successfully with succinyl sulfathiazole Dysentery bacilli disappeared from the stools of five carriers during succinylsulfathiazole administration and remained absent for periods of thirty to sixty days

H JOCELYN SMYLY

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ASIATIC CHOLERA

(*Cholera Indica*)

Definition —Cholera is an acute specific infection involving primarily the ileum It is characterized by profuse effortless diarrhea vomiting collapse muscular cramps and suppression of urine

History —The disease has existed in India from time immemorial Invasion of other countries however did not occur until modern times the first widespread epidemic in the Orient occurring in 1817 With the increase in travel and with little knowledge of epidemiology great pandemics arose in which cholera traveled to Europe by either of two main paths (1) overland to Russia by the caravan routes or (2) by water along the trade routes of Arabia and Egypt From Europe the disease has invaded North America, and has several times appeared on the eastern seaboard and along the Mississippi Valley Cholera has not yet been carried from the Asiatic coast across the Pacific Ocean to our western seacoast

Etiology —During the pandemic between 1879 and 1883 Koch working in Egypt described the cholera vibrio In view of the insusceptibility of lower animals to cholera he was unable to apply his postulates for

Sodium sulfate in saturated solution (30 per cent) should be given in doses of 4 to 8 cc (1 to 2 drachms) every two hours day and night when the patient is awake and continued for twenty four hours or until free watery stools are passed It can then be administered once every four hours This greatly relieves the pain and tenesmus Although some physicians are opposed to it sulfate of sodium or magnesium is almost universally used in countries where dysentery is common In children or in adults suffering from dehydration sulfates must be given cautiously together with abundant fluids both by mouth and parenteral injection Normal saline subcutaneously, glucose 5 per cent in normal saline intravenously, and blood transfusions should be used as indicated As acute symptoms diminish it is important to prevent retention of feces by continuing salines or by colonic *lavage Progress at this stage is sometimes* delayed for no apparent reason and lavage of the colon with normal saline at a rectal temperature of 40° to 46° C is beneficial Chinioform (yatren) by the mouth or by rectal injection is also useful in delayed convalescence

In the treatment of children the great essential is to combat dehydration and acidosis Guy and Yeh stress the importance of replacing minerals and vitamins as well as fluids They give cabbage water with com*mon salt and calcium lactate* Scott in Tsinan has found that sodium sulfate gives good results in children provided abundant fluid from 1 to 2 liters of normal saline every twenty four hours is given to the child Sodium sulfate is prescribed in 25 per cent solution 5 cc of which is given from 2 to 5 times in twenty four hours It lessens tenesmus and blood in the stools

In fulminating cases it is above all necessary to forestall collapse by keeping the patient warm and by intravenous injections of normal saline—amounts up to 1000 or 2000 cc (40–60 ounces) In the choleraic type Roger's hypertonic saline (sodium chloride 8 Gm—120 grains calcium chloride 0 25 Gm—4 grains water to 568 cc—1 pint) *may be given* intravenously

Serum therapy is still a matter of experiment and discussion The general opinion is that serum is antitoxic rather than bactericidal and that it is more effective in Shiga than in Flexner injections It should be *reserved for severely toxic* cases and given early in the disease A dose of 40 to 80 cc is given intravenously once or twice daily with the usual precautions against anaphylaxis it may also be injected into the muscles In the writer s experience large doses are necessary and should be continued for some days until the stools are decidedly improved and both temperature and pulse have returned to normal

The treatment of *chronic dysentery* calls for patience and perseverance but no case need be considered hopeless The usual treatment by injection of mild or dilute antiseptics into the colon is practically useless in most cases Contrary to the general belief dysentery bacilli persist in chronic cases for years and the patient does not get well until they are eradicated Various methods *may be employed for this purpose* Silver nitrate in 1 to 5 per cent solution is advised by C F Martin and is effective, but safer more satisfactory and less expensive is Dakin's solution Commencing with 25 per cent Dakin s solution 300 to 500 cc at body temperature are injected per rectum thrice daily The concentration is increased according to the patient's tolerance up to full strength Dakin s solution It is essential that the solution reach as high in the colon as the disease process and it should there*fore be given in the knee chest* position if the patient is strong enough and in some cases a larger volume of solution is necessary If this is not successful surgical assistance is indicated, as described below Yatren is also curative and is much less trying to the patient It should be given as a combined oral and rectal treatment An efficient dose is 0 5 Gm thrice daily by mouth and 3 Gm in 200 cc of water by rectum The rectal injection preceded by a cleansing enema is best given at night and is easily retained until the following morning in most cases

Hot normal saline lavage of the colon at a temperature in the rectum of 40° to 46° C is of value in subacute and chronic cases

Progress of the case while under treatment should be observed by repeated sigmoidoscopy If the rectum alone is ulcerated 10 to 20 per cent solution of silver nitrate

with shreds of mucus and cellular débris Occasionally, though rather rarely this material is very finely divided so that it does not settle out and thus forms the characteristic rice water stool Shortly after the onset of the diarrhea persistent vomiting usually occurs The subsequent symptoms may be divided rather sharply into two groups—those of collapse and those of reaction

Symptoms of Collapse—A characteristic train of symptoms sets in which is closely associated with the loss of fluid from the tissues The skin loses its elasticity muscular cramps become severe, the eyes sunken the voice feeble the thirst intense the secretion of urine ceases and the respiration becomes rapid The pulse is rapid and weak the blood pressure falls and the heart sounds are feeble The skin and mucous membranes are blue and the temperature of the skin is subnormal The rectal temperature may be subnormal in algid patients but rises slowly as the stage of reaction approaches

The loss in the elasticity of the skin is first noticed over the extremities The skin of the hands may wrinkle spontaneously (the washerwoman s hand) or when a fold of skin over the back of the hand is lifted it does not spring back into position but sinks down very slowly by its own weight Paradoxically well marked wrinkling of the skin develops either after the rapid loss of fluid or the soaking of the hands in water Muscular cramps appear first in the extremities as the loss of fluid is felt there first of all Native patients commonly tie bamboo thongs around the fingers and toes with the idea of preventing the cramps from spreading upward As the cramps increase in severity additional thongs are bound around the knee and elbows Indeed when such patients are admitted to the hospital it is at once evident that the symptoms have been unusually severe and that the need of fluid is urgent The patient either loses his voice completely or is able to speak only in a hoarse whisper The secretion of urine diminishes rapidly and often ceases altogether on account of the great loss of fluid the blood pressure in the renal artery may sink below the point (40 mm of mercury) which is necessary for the secretion of urine The blood pressure falls so low that on incising a superficial vein such as the external saphenous, a few drops of dark thick blood exude but no free hemorrhage occurs The red cell count is increased by 1,000 000 or 2 000 000 per cubic millimeter on account of the concentration of the blood The white cell count rises to 25 000 and even to 50 000 or 60 000 per cubic millimeter The exact nature of the polymorphonuclear leukocytosis is unknown The poor circulation and the consequent poor aeration of the blood stimulate the respiratory center and the respiration becomes shallow and rapid The pulse rate increases the temperature remains low—a condition which is exactly opposite to that of typhoid fever with its high temperature and relatively slow pulse Some cases terminate fatally during the first few days or even hours of the disease

Symptoms of Reaction—Distinctly more than half of the patients ordinarily survive the period of collapse or as it is often called the *algid stage* The signs of reaction are largely the reverse of those of collapse The diarrhea subsides and constipation may develop The muscular pains cease the skin becomes warm and elastic the voice returns and the body temperature rises The cyanosis gives way to a bright color of the skin and mucous membrane The respirations become deep and nearly normal in rate The pulse instead of being feeble and rapid returns to an almost normal rate and it may become full and bounding The blood pressure may rise to 150 or 160 mm of mercury at systole

Interest at this stage centers largely on whether the secretion of urine commences In some patients the amount secreted returns more or less gradually to normal and a satisfactory convalescence ensues In a relatively small proportion the evidences of toxemia persist and the patient passes into a typhoid like condition which may prove fatal

Acidosis and Uremia —During the stage of reaction the secretion of urine is resumed in the majority of cases but the daily output is small (100 to 300 cc) the specific gravity is high and albumin and casts are abundant The total output may increase slowly or may diminish and then cease altogether Uremia not unlike that of ordinary nephritis proves fatal in about 15 per cent

determining the etiologic relationship of an organism to a given disease and some un certainty arose concerning the causative role of this vibrio in cholera Doubting the patho genicity of the cholera vibrio Pettenkofer and Emmerich in 1892 drank a small quan tity of a bouillon culture Pettenkofer devel oped a mild diarrhea and the vibrios were recovered *from the watery stools*, but he maintained his skepticism concerning their etiologic role Emmerich developed a severe attack of cholera which nearly cost him his life Aside from this experiment there have been several accidental infections with the cholera vibrio The presence of virulent strains of *Vibrio cholerae* in the intestinal tract, however, does not always lead to the development of symptoms

Bacteriology—*Vibrio cholerae* grows readily on simple media, particularly if the reaction is neutral or slightly alkaline It is easily stained and is decolorized by Gram's method The organism is readily killed by heat drying, and disinfectants In freshly *isolated cultures the vibrios are extraordi* narily motile

The cholera vibrio is imitated precisely in its morphology *staining and cultural char* acteristics by vibrios which are found in the intestinal tract of man and also as free living *forms in nature At the height of an epid* emic the characteristics of the 'true chol era vibrio are well marked and it can be distinguished from other vibrios by the utili zation of Pfeiffer s phenomenon or by agglu tination tests with a specific serum prepared from a known strain of cholera Nonagglu tinable vibrios predominate during the inter epidemic periods and they are also found in the early and late stages of an active out break of cholera their relationship to the agglutinable strains is still unsettled The injection of moderate amounts of a cholera culture into the tissues of experimental ani mals such as guinea pigs or monkeys pro duces death in a few days but does not produce the clinical syndrome of cholera the ingestion of cultures by lower animals produces no effect except under highly arti ficial conditions

Epidemiology—For its propagation in nature *Vibrio cholerae* as far as we know depends entirely upon man The organism soon dies out in nature in competition with free living forms and is not har bored by any of the lower animals At the beginning of an outbreak, both the symp toms of the patient and the accompanying vibrios are often atypical, as the epidemic progresses, characteristic symptoms develop and the vibrios agglutinate typically The interepidemic periods are probably bridged over in part by human carriers but the pro portion of carriers after an epidemic is not large and the carrier stage is of relatively short duration This explanation of the in terepidemic periods is not especially satis factory and it is evident that the nonagglu tinable strains of vibrios must be given serious consideration

Seasonal Variation—A warm and moist climate favors the spread of cholera

Morbid Anatomy—An early and extreme grade of *rigor mortis* occurs in cholera A dusky cyanotic color of the skin, the finger nails, and the mucous membrane is notice able On incising the abdominal wall one is struck by the dryness and deep color of the tissues Instead of a little free *fluid in the* peritoneal cavity and the other serous sacs only a sticky residue remains The urinary *bladder is empty The ileum* particularly the lower portion may be reddened As a rule the ileum contains an abundant amount *of rice water material* though its contents may vary from a little bile stained mucus to dark purple blood tinged fluid The lymphatic tissue is prominent Histologi cally there is a subepithelial edema of the small intestine *Antemortem* desquamation of the epithelium is rare The renal lesions are mild in proportion to the severity of the uremic symptoms The kidneys often show parenchymatous swelling with an irregular cortex and distorted striations The wet brain of uremia is sometimes encountered Invasion of the gallbladder is common in fection taking place by direct *extension* from the duodenum

Symptoms—The *incubation period* is *short* but *variable ranging from* a few hours to five or six days

Onset—The disease may be ushered in with a preliminary warning which consists of one or two days of diarrhea or the onset be sudden with violent purging As the fecal matter is quickly cleared from the bowel the stools consist of almost clear water

ries distinctly not only in different epidemics but during the course of a given epidemic, being greatest as the outbreak reaches its peak Under ordinary conditions with patients coming under treatment rather late in the stage of collapse a mortality of 50 per cent may be expected but in exceptionally severe circumstances the death rate may be even higher Of this number about 30 to 35 per cent die in the stage of collapse and it may be expected that 15 per cent will die of uremia unless alkalis are used intensively Under more favorable circumstances when the patients report early for treatment the mortality may be restricted to 20 or 25 per cent

Prophylaxis —Cholera is spread in much the same general manner as typhoid fever The vibrios leave the body by way of the feces and the vomitus Epidemics and pandemics of cholera have arisen with a severity unknown in typhoid fever and at times these outbreaks have spread with terrifying rapidity However the disease cannot travel any faster than man travels and an outbreak is usually amenable to preventive measures

Control of an epidemic of cholera can be brought about by (1) protection of the supplies of food and water from contamination (2) destruction of the excreta of patients (3) prophylactic inoculation for reducing the susceptibility of the population The individual can protect himself with comparative ease in times of an epidemic The recommendation to use only *hot food* and *drink* is particularly good The vibrios are easily killed by heat but food and water though properly heated may after cooling become seriously contaminated in a very few hours. In several tropical communities the public has been instructed thoroughly in preventive measures and the educated adult who contracts cholera frequently receives little sympathy from the community in general

For *specific protection* against cholera suspensions of vibrios killed by heat may be injected subcutaneously without any more inconvenience to the individual than if sterile saline had been used It is probable that a moderate degree of protection exists for a few months after inoculation This in itself would be of great assistance in controlling an epidemic The vibrios are limited almost entirely to the intestine and the theoretical basis for vaccination is less evident than in typhoid fever

Attempts have been made to protect communities by treating the water of village wells and cisterns with vibriophage

Treatment —There are three objects to be accomplished in treatment namely, (1) the relief of toxemia (2) the restoration of fluid (3) the prevention of acidosis and uremia

Many *specific antitoxic sera* have been prepared for cholera but they have not proved of value Until the nature of the toxemia is understood it will be difficult to provide specific treatment Attempts have been made to utilize vibriophages for specific therapy and the idea has been advanced that only those patients recover who receive phage or who develop their own phage This view has not yet been established

The *restoration of fluid* is undertaken by intravenous injection of salt solution Usually 2 liters of saline are given in the course of fifteen or twenty minutes The immediate effect is striking the blood pressure rises the pulse and respiration become slower the skin becomes less cyanotic and resumes its elasticity the patient instead of tossing about restlessly lies quietly and comfortably in bed the voice returns The first request is usually for a glass of water This does not mean that the injection of saline has made the patient thirsty but rather that with increasing comfort he is able to make his wants known Very few of these patients however proceed to an uninterrupted recovery On the contrary the profuse diarrhea continues and unless the supply of fluid is maintained the symptoms of collapse return often with increasing severity An average patient requires the intravenous injection of 2 liters of fluid every six or eight hours for one or two days Some patients apparently moribund may require injections of this amount of fluid every two or three hours for a day or more One of the gratifying features of treatment is that apparently hopeless patients may unexpectedly react and make an uninterrupted recovery On one occasion a patient who was semicomatose on admission received 28 liters in the first twenty four hours he then reacted satisfactorily and

of all patients who contract cholera It was first shown in Asiatic cholera that uremia is closely associated with acidosis The carbon dioxide content of the blood diminishes markedly and the tolerance to sodium bi carbonate is greatly increased In the midst of an epidemic the clinical course of cholera is fairly uniform The severity of the disease and the mortality rise to a peak during an epidemic and then decline As already noted a small percentage of individuals though in fected with virulent vibrios, develop no symptoms Occasionally a prodromal diar rhea develops without consequent severe symptoms Rarely the disease proves fatal without diarrhea In this condition known as *cholera sicca* the bowel at autopsy is fre quently filled with rice water material In young children the symptoms are less se vere and the mortality is lower than in adults A slight but definite meningismus is of frequent occurrence though the meninges remain free from any infection

Cause of Symptoms —There is no evi dence that cholera vibrios produce a potent soluble toxin *in vitro* and the assumption of an endotoxin acting *in vivo* rests on hypo thetical grounds However cholera vibrios multiply high up in the ileum where ordi nary bacteria do not colonize and there is experimental evidence of the formation of toxic proteoses in the algid stage of cholera It has been suggested that desiccation may account for all of the symptoms including the signs of toxemia In this connection it is interesting to note that travelers lost in the desert may develop symptoms suggestive of the collapse of cholera Under these circum stances the restoration of fluid usually pro duces prompt and permanent relief in con trast to the temporary benefit observed in cholera The extremely rapid loss of water and salts from the tissues presents an oc casion for the study of the effects of dehy dration and of salt imbalance that is quite unequalled by clinical opportunities avail able in other infections

Complications and Sequelae —Asiatic cholera does not produce destructive lesions and ordinarily leaves no serious aftereffects although in American and European pa tients the return to full health and vigor may be protracted over several weeks or months Just as in acute nephritis from other causes the renal lesions do not become chronic, indeed, normal renal function is often restored quickly Cholera usually causes abortion, the muscular cramps which appear first in the extremities develop also in the uterine musculature The intestinal lesions heal readily and no after period of diarrhea or constipation is to be anticipated In the great majority of cases the vibrios disappear promptly from the stools A small but important number of patients remain carriers for weeks and even months but not for years

Diagnosis —During an epidemic any pa tient who suddenly develops coma or col lapse should be sent to the cholera hospital for observation Acute diarrhea following poisoning by alcohol, or mushrooms or accompanying food poisoning so called requires differentiation In these conditions vomiting usually precedes the diarrhea whereas the reverse is true in cholera An accurate diagnosis can be made only by bacteriologic methods Since agglutinins ap pear in the blood rather late in the disease reliance is placed on the isolation of cholera vibrios from the stools and their identifica tion by agglutination with a specific serum The vibrios occur in such great numbers in the stools and grow so rapidly that routine diagnoses are easily obtained in twenty four hours The usual method for the examina tion of stools consists in the inoculation of peptone water with a little rice water ma terial The vibrios if present grow abund antly near the surface of the liquid After eight hours it is sometimes possible to make an agglutination test directly on this fluid culture though it may be necessary to sub inoculate this enriched material on an agar plate and examine individual colonies

For the examination of carriers a selective medium is very helpful The standard me dium for this purpose is a very strongly alkaline blood agar (Dieudonné s) This allows free growth of various vibrios and of some of the streptococci but restrains ef fectively the great mass of fecal bacteria In the examination of carriers it is impor tant not to use purgatives for after taking magnesium sulfate carriers have been known to develop a typical fatal attack of cholera

Prognosis —The mortality in cholera va

plague appears to be confined to regions where the climate is temperate by virtue of latitude or elevation A relationship between plague in man and plague in wild rodents was first demonstrated by officers of the United States Public Health Service near San Francisco California in 1908 It has been assumed but not proved that the infection of the wild rodents in California was a sequel to the introduction of plague into San Francisco from the Orient in 1900

Subsequently, the existence of sylvatic plague has been demonstrated in many counties of California and in parts of twelve of our Pacific and Mountain States (Meyer 1942) Important recent information on sylvatic plague in the United States has been published by the United States Public Health Service and by Meyer Sylvatic plague is chiefly of importance as a source of infection for house rats which may then initiate outbreaks of the disease in man It is probable that sylvatic plague is spreading in the United States and that its true extent in this country and elsewhere is still unknown Only 40 human cases of plague in the United States had been attributed directly to infection from sylvatic sources up to 1938 (Eskey 1938)

Etiology and Epidemiology —Infected rodents through the agency of their ectoparasites constitute the reservoirs from which bubonic plague spreads to man and occasionally to other animals either wild or domestic Epidemics of plague in man are *generally preceded by epizootics* in house rats or mice but outbreaks of human plague in South Africa in Argentina in Russia and in China have been attributed directly to sylvatic sources Wild rodents of various genera including ground squirrels marmots gerbilles and cuis (related to the guinea pig) are subject to plague Plague travels in infected rats which frequently accompany shipments of grain by land or water

The distribution and seasonal prevalence of plague are determined largely by local and seasonal prevalence of the chief vector *Xenopsylla cheopis* the rat flea Various other kinds of fleas which attack rodents are capable of transferring plague to man and other biting insects are suspected of transmitting it occasionally That plague can be transmitted to man by *Pulex irritans* is considered probable by some authorities and doubted by others The Plague Commission of the Government of India in 1908 reached the conclusion that ingested food plays no part in the spread of the plague in nature, either from rat to rat or from rat to man Furthermore the experiments of this Commission seemed to prove that neither direct contact with cases of bubonic plague nor with fomites contaminated with the excreta of such cases was dangerous

A varying but usually small proportion of cases of primary pneumonic plague occurs along with epidemics of bubonic plague Probably these cases originate from bubonic or septicemic cases in which pulmonary lesions have developed Primary pneumonic plague is very readily transmitted directly from man to man through the agency of droplets expelled by coughing

Control.—Since the establishment of international quarantine regulations plague has disappeared from many of the seaports in which it used to be common Epidemics of bubonic plague are controllable by quarantine isolation of cases and suspects and destruction of rats and their parasites Control of pneumonic plague presents no great difficulty except under such conditions as occurred in Manchuria during the winter of 1910–1911 (Strong *et al* 1912) At that time very cold weather overcrowding in the homes of the poor and other unsanitary conditions combined to favor the spread of this form of the disease Efforts to exterminate rats and their parasites are of short lived value unless accompanied by wholesale rat proofing of dwellings warehouses and other buildings in which rats breed Information about this from Java was published in an official report by Rosier (1937) Campaigns of destruction of wild native rodents subject to plague in California as yet afford no hope of the eradication of the sylvatic infection in the United States

Although extensively used in India for many years the Haffkine vaccine which is made from killed cultures has proved unsatisfactory as a means of limiting the spread of plague Otten (1940) and other workers have reported good results from the use of a vaccine containing attenuated living plague bacilli A single dose of this vaccine is said to produce a higher degree of immunity in

made an uninterrupted recovery The inspection of the patient, the character of the pulse, and the amount of fluid lost by the bowel serve as adequate guides for the frequency of injections Various tests have been devised for this purpose such as the determination of the specific gravity of the blood In the opinion of the writer, fluid should be supplied freely before the specific gravity of the blood is increased beyond normal limits

Acidosis and Uremia—The urine often remains sharply acid in cholera even after massive injections of sodium bicarbonate (90 Gm within twenty four hours) In a normal person 5 Gm of bicarbonate ordinarily renders the urine alkaline Investigation has demonstrated the existence of an acidosis in the sense that the fixed bases of the blood and other tissues of the body are depleted Prompt restoration of these bases leads to significant results in the treatment of patients During the stage of collapse a slightly alkaline solution (0.5 per cent sodium bicarbonate and 0.5 per cent sodium chloride) may be used intravenously As the stage of reaction sets in the quantity of bicarbonate should be increased (to 1 5 or 2 per cent) and the chloride omitted The injections of bicarbonate should be continued until the urine becomes alkaline or until it is very liberally secreted Instead of the expected mortality of 15 per cent from uremia the early and persistent use of alkalis has practically eliminated death from uremia in private practice where patients report promptly for treatment A mortality from uremia as high as 4 per cent may occur in hospital practice with its proportion of patients admitted in late stages of infection

General Measures—The patient is naturally glad to remain in bed During the algid stage hot water bottles and light blankets afford the much desired warmth The vomiting which during the first days of the disease prevents the administration of even water by mouth may be checked temporarily by small doses of *cocaine* (⅛ grain) by mouth *Digitalis* is very useful in regulating the action of the heart During the period of convalescence small amounts of liquid food are given but solids should be added

A W SELLARDS

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PLAGUE

Definition—Plague is an infectious disease caused by *Pasteurella pestis* the *Bacillus pestis* of Yersin It is primarily a disease of rodents and the several species of the rat which frequent human dwellings and warehouses are susceptible

Geographic Distribution—According to Wu Lien-Teh (1936), central Asia is probably the original home of plague, and the present pandemic first gained momentum on reaching Canton and Hongkong in 1894 He believes that Africa, the Philippine Islands Australia and the Americas were first invaded since that date According to his map of the distribution of plague in 1934 important active foci of bubonic plague existed in Transbaikalia (Manchukuo), in Shansi Shensi and Fukien provinces in China and in Burma, Siam, Indo-China Java India and Ceylon

Figures on the incidence of plague in 1941 and 1942 which have been published in the Reports of the United States Public Health Service are far from complete Comparatively few cases of plague were reported from China during the period Considerable numbers of cases occurred in British East Africa Morocco Madagascar the Dutch East Indies and India and there were significant numbers of cases in Brazil Argentina and Peru

The history of plague in the Americas has been presented by Moll and O Leary (1940) and they have provided detailed information about the disease in various Latin American countries (ibid 1941 and 1942)

Sylvatic plague signifies plague which is enzootic in rodents other than those of domestic habit It occurs particularly in sparsely populated regions where at intervals of years it causes explosive outbreaks among burrowing rodents Thus far sylvatic

temperature to about 120 or over, and the respiration rate to 30 or 40 per minute Co incidentally the malaise increases there may be vomiting or diarrhea and pain be comes severe at the site of the developing bubo The face is drawn and anxious The tongue is furred and sordes appear on the gums and lips The gait becomes staggering and mental dulness and physical prostration are very pronounced There may be wild or muttering delirium The temperature curve is very irregular It generally shows marked morning remissions and in cases of recovery it falls after a few days by lysis In fatal cases it may shoot up suddenly or fall critically and then shoot up again to 107° F Rapidity of the breathing is pro nounced even though the lungs may show no more than scattered moist rales Pleuritis or pneumonia may develop secondarily

Herpes does not occur The spleen is easily felt as a rule and the liver may be palpably enlarged The abdomen is tender only when the intra abdominal glands are markedly enlarged The skin is hot and dry and often shows petechiae or ecchymoses Less frequently pustules vesicles necroses or a carbuncle are seen There may be hem orrhage from any of the mucous membranes or from the kidneys

The buboes generally become manifest within twenty four hours of the onset They may subside or suppurate Rarely the infec tion is first manifested by acute inflamma tion of the throat In such cases the buboes generally develop in the neck Some cases of bubonic plague are so mild that the patient may continue to walk about for several days or even through the entire course of the illness Such cases are apt to appear at the beginning of an epidemic or when it is subsiding Very rarely bubonic inflamma tion due to the presence of *Pasteurella pestis* may persist for several months Purulent encephalitis may occur and a case of chronic relapsing latent meningeal plague has been reported

In the primary septicemic type of plague the constitutional symptoms are the same as in the bubonic type This form of the disease usually runs a rapidly fatal course without the development of buboes Plague bacilli may be so numerous in the blood as to be demonstrable in stained blood smears

The primary pneumonic type of plague is characterized by the rapid development of a lobular pneumonia which becomes con fluent and thus produces extensive pul monary consolidations The sputum is blood stained but watery whereas in other kinds of pneumonia it contains much fibrin and is in consequence viscid and sticky Primary pneumonic plague is nearly always fatal within a few days Its incubation period is from one to three days

Clinical Diagnosis —The possibility of plague should be considered in the presence of an acute and painful adenitis not clearly due to venereal infection and such suspicion should lead to adequate bacteriologic exam inations One should be alert to the pos sibility of plague in seaports or other communities where plague has occurred The widespread distribution of infected rodents in rural areas in many parts of the world should not be forgotten There have been notable examples of failure to diagnose plague through failure to suspect its presence until after an epidemic was well under way

A venereal bubo can usually be differen tiated from plague by the presence of a soft chancre on the penis or by the hardness of the glands and the absence of sensitive ness which characterizes syphilitic adenitis Lymphogranuloma inguinale is common in the tropics and not uncommon in the tem perate zone Its onset is more gradual than that of plague constitutional symptoms are comparatively slight and the bubo is seldom very painful Bacteriologic examinations are entirely negative but the Frei test is usually positive

Tularemia and streptococcus infections may closely resemble plague Skilled bacte riologic examination is required to differen tiate them Acute infectious mononucleosis differs from plague in that its onset is more gradual the constitutional symptoms milder the adenitis less pronounced more general and less painful and the blood pic ture characteristic

The acute constitutional symptoms of severe typhus fever malaria or other over whelming infection may resemble those of septicemic plague Influenza pneumonia may simulate pneumonic plague but the character of the sputum serves to differen tiate them

man than two doses of a killed vaccine The mortality of individuals who have become infected after the vaccination is believed to be lower than in the unvaccinated Although living vaccines have been in use for several years and untoward effects from them have not yet been reported some doubt as to their safety is still justifiable

No form of vaccine confers complete immunity but the mortality in those infected has been decidedly lower in the vaccinated than in the unvaccinated Because the duration of the protective effect diminishes after a few months it seems advisable to withhold vaccination until exposure is imminent

It is probable that some degree of passive immunity lasting not more than a few days is conferred by the injection of antiplague serum Recovery from plague confers a degree of immunity which protects from a second attack or causes subsequent infection to run a mild course

Individual Prophylaxis—Persons likely to be exposed during an outbreak of plague should be vaccinated promptly Because infection may occur through an abrasion or perhaps through unbroken skin persons who examine the bodies of plague suspects carcasses or diseased tissues should do so with extreme caution They should wear rubber gloves These precautions should be observed also by physicians or others whose duties bring them into contact with suppurating lesions

Inasmuch as infection by ingestion seems not to occur it may not be necessary to disinfect the urine or feces of plague cases Because primary bubonic plague is frequently associated at some stage with pulmonary lesions it would seem desirable to isolate all cases of plague infection

Primary pneumonic plague requires extreme precautions against infection Any person attending these patients should wear a thick close fitting mask and goggles and a uniform which should afterwards be removed promptly and sterilized Rubber gloves are also recommended

In regions where sylvatic plague exists the most necessary precaution is to avoid contact with sick rodents and their parasites However inapparent plague infection has been shown by the United States Public Health Service to exist in rodents so that complete safety involves avoidance of all contact with them and with their parasites

Morbid Anatomy—A small vesicle or a carbuncular lesion may develop on the skin at the point of infection but such lesions are rarely seen The lesions found at autopsy in typical cases of bubonic plague are characterized by marked congestion and hemorrhagic edema of masses of lymphatic glands and particularly of the group of glands draining the region where primary infection occurred There is also edema and extravasation of blood into the periglandular tissue Such buboes are found in about 75 per cent of cases of plague The petechial spots which commonly occur on the skin and mucous membranes are caused by injury to the endothelium of the blood vessels Hemorrhages may occur also on the meninges in the brain or in the spleen Usually the heart is dilated and shows fatty degeneration The larynx, the trachea the kidneys and other internal organs show intense congestion The spleen is considerably enlarged in most cases The tonsils are not markedly inflamed as a rule Occasionally they are the seat of the primary infection The glands of the neck then show enlargement

The inflammation in primary pneumonic plague spreads from the bronchial mucous membranes to the peribronchial tissues and thence to the alveoli where it sets up a lobular pneumonia which later becomes confluent The glands at the bifurcation of the trachea are much more inflamed than are the lymphatic glands elsewhere

Symptoms—Three clinical types of plague are commonly recognized namely the bubonic the septicemic and the primary pneumonic

The bubonic type is characterized except in mild cases by very painful inflammation and swelling of the lymphatic glands of the groin the axilla or the neck In the great majority of cases the adenitis is most manifest in the groin The incubation period of this form of plague is from two to ten days There may be prodromal symptoms consisting of malaise headache giddiness and pain in the back and limbs Usually the onset is abrupt the temperature rises within a day or two to 103° or 104° F and there are attacks of shivering rather than pronounced chills The pulse rate rises with the

History.—William Burnett in 1814 published an excellent description of the disease commonly known as "the Bilious Remittent Fever of the Mediterranean" and recorded autopsy findings He distinguished between this disease and malarial fevers by the failure of the former to respond to bark infusions Marston in 1863 used the term Maltese fever for Mediterranean remittent fever which he differentiated from typhoid

Bruce isolated a coccoid organism from the spleen in 1886 and transmitted the disease to monkeys with the culture

In 1897 Bang isolated a similar organism as the cause of contagious abortion in cattle but it was not until 1918 that Evans recognized the relation of Bang s organism *Bacillus abortus* to Bruce s *Micrococcus melitensis*

Infection in man was first observed among goat herders and persons who consumed goat s milk, then among veterinarians and finally in the general population Bevan in 1922 noted cases in Rhodesia apparently connected with contagious abortion of cattle In 1924 Keefer described the case of a young man with unexplained fever from whose blood culture brucella organisms were grown It was thought at first that the patient contracted the infection from eating cheese but it was found later that he became infected probably by handling fresh tissues from hogs

Etiology—The exciting cause is a minute nonmotile gram negative pleomorphic organism appearing sometimes as a coccus and sometimes as a small bacillus growing slowly on first isolation and requiring special medium It does not ferment sugars It is very resistant to drying The three varieties are *Brucella abortus caprinus* (goat) *Br porcinus* (hog) and *Br bovinus* (cattle) The varieties differ in resistance to bacteriostatic dyes and immunologic reactions also strains in the same variety are not immunologically identical

Pathology—The changes found in general infections without specific lesions are described The liver and spleen bear the brunt of the infection In the liver in addition to the small areas of focal necrosis and small foci of reticulocytes and lymphocytes there are areas of endo and thrombophlebitis with discrete and confluent granulomata resembling tubercles The latter are found also in the spleen with exudative and sclerotic areas Occasionally there are small ulcers in the intestinal mucosa and small focal necroses with lymphocytic infiltrations in the kidneys and the lungs

Epidemiology—The reservoir of the infection is in goats cows and hogs Man contracts the infection by drinking unpasteurized milk or handling infectious material In man the organism is given off in the urine (10 per cent of cases) and in a few cases in the feces There are human carriers in the sense that in the chronic stage the organisms have been cultured from the stool in a few instances but no case has been traced to infection by a carrier The organisms have been recovered from human milk The organism is very resistant hence it is possible to contract the infection from butter and cheese made from contaminated milk

Cases occur in all ages except during the nursing period of infancy More cases are observed in males than females Veterinarians goat herders farmers packing house employees and laboratory workers are especially liable to infection

The disease occurs at all months of the year but is more frequent in summer probably because of heavier contamination of milk at this period In 1935 there were reported 1897 cases in the United States with the highest incidence in Iowa There are undoubtedly many more cases Of the organisms isolated from blood cultures abscesses urine and stool 70 to 93 per cent were porcine and the remainder bovine except for an occasional caprine strain from imported cases The porcine strain also infects cattle and is transferred to man by cow s milk As the porcine strain is more invasive for man than the bovine the infection may be transferred by milk containing a relatively small number of organisms whereas milk heavily contaminated by the bovine strain may not transmit the infection Pasteurization kills the organism

Symptomatology—*Incubation Period*—The time between exposure to a possible source of infection and the onset of actual symptoms has been observed to be from five days to one month but is usually about two weeks

Mode of Onset—UNDULANT TYPE—Mild symptoms of general malaise muscular and cervical pain anorexia and headache with evening fever gradually increase in intensity for about ten days after the manner of typhoid fever

Course of the Disease—As the temperature reaches 104° to 105° F the symptoms are intensified The patient is irritable and restless and there is marked sweating usually in the morning He complains of extreme weakness is in low spirits and cannot

Laboratory diagnosis depends ultimately upon the isolation of *Pasteurella pestis* A provisional diagnosis can be made in bubonic plague by puncturing the gland with a large needle, abstracting gland juice or preferably a little gland tissue, and staining it on a slide with Loeffler's blue or dilute carbolfuchsin *Pasteurella pestis* is a bipolar staining, ovoid organism After the gland has become soft, the organism may not be demonstrable except by culture

In cases of septicemic plague the organism may be demonstrable in blood smears and in pneumonic plague the sputum is loaded with them in almost pure culture *Pasteurella pestis* can often be cultivated on the usual laboratory media from the blood of man in cases of the bubonic type of plague even when mild Cultures and guinea pig inoculations can be made from gland juice blood or sputum The macroscopic lesions in the guinea pig the rat, or the mouse are, usually, characteristic but cultures should also be made from the test animals because various other organisms may produce plague like lesions in animals Similar difficulties may be encountered in diagnosing plague in other rodents Plague infected rodents may even show no pathologic evidence of disease Mass inoculation of organ samples or of rodent parasites into guinea pigs, may then be required to detect the presence of *P pestis*

Prognosis *—Mortality from the bubonic* type of plague commonly varies in different epidemics from about 30 to 75 per cent Individual cases may be fulminant or mild The prognosis is better for persons recently vaccinated Septicemic plague as a rule is rapidly fatal Primary pneumonic plague is almost always fatal Cases of secondary pneumonia in plague may recover

Treatment —Antiplague serum made from horses has long been used with some success in the treatment of bubonic plague Living and highly antigenic cultures are required for the production of active antiplague sera Serum therapy has yielded good results in bubonic cases when administered within the first few days of illness With each succeeding day the chance of benefit decreases until the fourth or fifth day after which serum is useless It is useless also in primary pneumonic and septicemic cases

Doses of 30 to 40 cc administered intravenously seem to have given good results Larger doses of 100 to 250 cc have been recommended but, when given intravenously these large doses may cause serious circulatory disturbances The dose is to be repeated, when needed, after six or eight hours

Decidedly encouraging results were obtained by Norman Walker in 1937, using serum of convalescent patients The use of iodine whether by mouth or intravenously seems to be without benefit Use of the sulfonamide derivatives is in the experimental stage Wagle *et al* (1941) believe that mortality can be significantly reduced by the use of sulfapyridine or sulfathiazole

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BRUCELLOSIS

(Undulant Fever Malta Fever Mediterranean Fever Goat Fever Dust Fever)

Definition —An acute and chronic disease of varied duration with protean manifestations characterized by fever weakness sweating and aches caused by general infection with a member of the abortus group *of micro organisms*

leading to unnecessary operation orchitis less commonly prostatitis and vesiculitis

Other Clinical Varieties—Brucellosis is protean in its manifestations There is great variation in the clinical picture exhibited by cases contracting the infection from apparently the same source

Brucella Infection of Short Duration—The fever may last only six days but the weakness and irritability may endure for weeks The diagnosis is made by blood culture It is probable that many of these cases escape diagnosis and are regarded as influenza

Ambulant Type—A large number of infected persons although feeling somewhat ill with slight feverishness fatigability weakness and headache continue to work The diagnosis is made later by the presence of a high agglutination reaction or positive skin reaction

Asymptomatic Type—Huddleson and Johnson found agglutination titers from 1 50 to 1 500 in the serum of twenty eight out of forty nine veterinarians examined Only three of them gave a history of past illness which resembled brucella infection In addition the serum of two students had agglutinins of 1 200 and 1 500 with no symptoms except a cold and tonsillitis in one of them

McBryde studied the serum of children in an orphanage where infected milk was used There were a certain number who had no illness but agglutinins of significant titer were found in their serum and continued to be present so long as contaminated milk was served The agglutinins disappeared when pasteurized milk was used Dooley has also studied the agglutinins in subclinical cases

Cases with Recurrent Mild Symptoms—A very mild form of the undulant type may not be recognized as brucella infection but be mistaken for psychoneurosis tuberculosis endocarditis or malaria Complications from brucella do occur in these cases and often the diagnosis is made only after an intensive study

Temperature Curve—The undulant type consists of several waves of fever similar to those of infectious mononucleosis In other cases the temperature may be sustained with occasional dips or it may simulate the curve in typhoid fever or malaria In the chronic stage the temperature may not exceed 100° F even when the blood culture is positive

Complications—Arthritis often occurs during the acute and chronic stages Baker found brucella in the joint fluid of a case of double recurring hydrarthrosis of the knees The original mild attack occurred seventeen years previously

A case of brucella spondylitis simulating Pott s disease has been reported Various long bones and in 1 instance the small bones of the wrist have been involved D T Smith reported a case of brucella meningitis with recovery Endocarditis is not infrequent and may simulate in every way subacute bacterial endocarditis Pericarditis has been reported in one of these cases and mycotic aneurysm of the basilar artery was discovered at necropsy in two cases Amoss likewise Gilbert and Coleman have isolated brucella from aspirated bile A culture from suppurative cervical lymphadenitis simulating tuberculous infection yielded brucella

Brucella has been isolated from the urine in cases with initial symptoms of cystitis and renal tuberculosis and from uterine discharges following abortion Amoss reported a case of chronic brucella peritonitis with tuberculous salpingo-oophoritis and a case in which this organism was recovered from a small cyst on an otherwise normal ovary Mastitis is not an infrequent complication Chronic subcutaneous abscesses have yielded a pure culture of brucella in several instances The organism has been isolated once from pleural fluid Uveitis as a complication has been observed frequently in epidemic areas

Diagnosis—In acute cases a tentative diagnosis is often made by the clinical signs already enumerated and is confirmed by blood culture To avoid the inhibitory effect of the patient s serum a small amount of blood is placed in a large amount of liver broth A flask and plate should be incubated also in 10 per cent CO_2 Growth may not be apparent for eight or more days Before discarding as negative the cultures should be incubated for eighteen days Intermittent bacteremia may be present even when there is very low grade fever hence repeated blood cultures may be necessary

sleep The tongue is coated but the edges and tips are clean Constipation is usually marked and there is often a slight bronchial cough The pulse rate is generally consistent with the fever but relative tachycardia or bradycardia may be present Dicrotism is rare Slight leukopenia is the rule with diminution especially in the myeloid elements and relative increase in mononuclears, some of which may be pathologic The white count in some cases may be very high with a marked increase in small lymphocytes The spleen may be slightly enlarged to percussion and in a small percentage of cases is palpable The clinical picture with leukopenia catarrhal symptoms and occasionally epistaxis or intestinal hemorrhage may at this time suggest typhoid fever but the apathy, headache red tongue and rose spots are absent Moreover, within a day or so the temperature begins gradually to decline and there is a slight clinical improvement Another feature which is useful in arriving at a tentative diagnosis of undulant fever is the sudden appearance in the majority of cases of intense sacro iliac pain or sciatic neuritis which endures for three or four days Joint pains with tenderness and swelling especially of the knee ankle hip and shoulder are often present and last for a day or so to return in the later phases of the disease

Blood cultures with special technic for *Brucella* are positive Incubation for at least ten days is necessary and frequent transfer to solid medium during this period determines the presence of organisms

Agglutinins to one or more stock strains of brucella usually appear in the patient s serum after the first week but may be absent throughout the course of the disease It is important to set up high dilutions as the proagglutinoid zone may be present in as high a dilution as 1 1200 If the titer is below 1 100 serum should be taken five to seven days later for a retest If the reaction is then present in higher dilutions the test is of significance Because of the great antigenic differences in the members of the brucella group several stock strains (at least three of each variety of *Brucella abortus*) should be used Cases have been observed in which agglutination was positive with only one of eleven antigens used in testing Agglutinins may be absent or they may disappear during the course of the disease On the other hand they may reach a dilution of 1 20,000

Subsequent Course—The fastigium is very brief The fever curve from the onset reaches a higher point each evening and the morning remission is less As the evening temperature reaches 104° to 105° F it then begins within a day to decline until the temperature is normal and the constitutional symptoms have almost disappeared The whole febrile phase lasts about three weeks After a day or so of normal temperature fever recurs with exacerbation of the other constitutional symptoms There may be only two such waves or they may recur for a period exceeding a year The average length of an attack of the undulant type is about three months

The undulant type results not only from infection with the caprine strain of *Brucella* as seen in the Island of Malta and in the Pecos Valley of Texas but also with the porcine and bovine strains now being observed all over the United States There is great variability among the caprine cases but in general the bovine strain seems to produce a milder type of infection than either the caprine or the porcine The great majority of cases in the United States are of porcine origin, with the remainder bovine Caprine infection in this country is rarely observed except in Texas and Arizona

About 15 per cent of the cases in the United States are of the undulant type In general the first wave of the undulant type is like an attack of influenza while in the second wave there is intensification of symptoms with headache constipation and insomnia Sweating may be present in the first wave but usually does not appear until the second wave Stitt in contrasting the infection of caprine origin with the cases of porcine and bovine source as seen in the United States notes the following outstanding features in the latter group remarkable absence of physical signs (including infrequent splenomegaly), profuse redolent sweating loss of body weight fatigability with absence of prostration joint manifestations and neuralgias not so common or severe abdominal pains more prominent even

devoted to the mental depression which accompanies the infection

Specific treatment is not yet on a firm basis The sulfonamides have been used with apparently good results in a few cases but on further trial have been disappointing

In acute cases with low agglutinin titer Foshay's goat or horse antiserum is given intravenously or subcutaneously after testing for sensitivity in 20 cc doses daily for five days or until there is evident improvement The average amount of serum given is from 90 to 120 cc Serum therapy is not advised after the eighth month of the disease As the response to serum treatment is uncertain the possibility of added discomfort by serum sickness must be taken into account

In prolonged cases frequent small transfusions of 250 cc by the indirect method are advised The use of donors who have been immunized against brucella is a logical procedure

Vaccines may be given in the chronic or recurring type especially when the agglutinin titer of the patient's serum is low Systemic reactions may be severe It is well to begin with 0 1 cc of a 1 100 dilution of the vaccine and increase the dose guardedly and according to the severity of the reaction The vaccine is given intracutaneously at five-day intervals

Brucellin the nucleoproteins of the organism in a mildly alkaline solution has been used successfully by Huddleson It may be used with care in selected cases Some patients have marked constitutional reactions to small doses while others may be given as much as 1 cc without discomfort The positive skin test with brucellin denotes sensitivity to the nucleoproteins In cases in which the agglutinins and cytophagic index are high and the skin test with brucellin is markedly positive the patient should be desensitized by graduated injections of brucellin The series of injections begins with 0 1 cc intracutaneously and is repeated at five day intervals increasing the amount by 0 1 or 0.2 cc until 1 0 cc is given A dilution of 1 10 is then employed in like manner

In cases of long duration search should be made for localization especially in the gall bladder or prostate If treatment with sulfapyridine combined with daily diathermy through the site of the localization is not effective surgical excision is indicated

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PERTUSSIS

(*Whooping Cough French coqueluche German Keuchhusten Italian pertosse Spanish tos ferina*)

Definition—Pertussis is an acute infectious disease of the respiratory tract characterized in its typical form by a series of repeated spasmodic coughs followed by a sudden forceful inspiration (the whoop) and sometimes by vomiting Since the disease may exist without the whoop and since other infections of the respiratory tract may be associated with this symptom the name pertussis is preferred to that of whooping cough

Historical—Although the earliest reference to the disease was probably made by Moulton in 1540 De-Baillou in 1578 is credited with the first classical description of pertussis As quoted by Major DeBaillou discussed the disease in part, as follows "Principally that common cough which is usually called Quinta or Quintana which has been mentioned before Serious are the symptoms of this The lung is so irritated so that every attempt to expell that which is causing trouble it neither admits the air nor again easily expels it The patient is seen to swell up and as if strangled holds his breath tightly in the middle of his throat." "For they are without this troublesome coughing for the space of four or five hours at a time then this paroxysm of coughing returns now so severe that blood is expelled with force through the nose and through the mouth Most frequently an upset of the stomach follows nor have I read any author who has made mention of this cough

Incidence—Pertussis is sporadic and endemic to the more thickly populated communities throughout the world Epidemics

After the first week agglutinins may be present, but often they are not found at all, or not until late in convalescence If agglutinins are not demonstrable in a suspected case, a skin test with 0 05 cc of 1 500, or 0 1 cc of 1 1000 solution of *brucellergin* read after forty eight hours will often prove valuable A positive reaction indicates present or past infections with *Brucella* and denotes a hypersensitive state to the nucleoproteins of this organism To determine whether the positive skin test results from active or inactive *Brucella* infection the phagocytic test of Huddleson is necessary A positive phagocytic reaction is found in the immune, or inactive state a negative reaction in the presence of a positive skin test denotes active infection

At the present time, with typhoid fever on the wane and increasing incidence of brucella infection, the clinician should be mindful of the latter disease in any case of fever of unknown origin

Differential Diagnosis—There are no pathognomonic signs in brucella infection The acute onset is usually more gradual than in *typhoid fever* and the effect on the sensorium less marked The fastigium is usually very brief and the abdominal signs and symptoms are mild In both diseases there is prostration but in brucellosis the sweating is usually pronounced especially in the second wave while it is absent in typhoid fever The usefulness of cultures in differentiating these diseases is obvious Commonly there is a definite leukopenia which suggests either typhoid or *influenza* The differential diagnosis between brucellosis and influenza is sometimes difficult because of the prostration and general aching sweating and leukopenia in both diseases Influenza is of shorter duration more abrupt in onset and there are usually evidences of upper respiratory infection The typhoidal type of *tularemia* with absence of clinical signs may simulate brucellosis especially if cross agglutination is reported as sometimes happens The insidious onset in some cases with weakness loss of weight, anorexia sweating and low white count suggests *tuberculosis*

Brucellosis may be confused with *malaria rheumatic fever* and *pyogenic infections* but appropriate observation and study differentiate them

On account of the abdominal pain and tenderness cases of brucellosis have been diagnosed as *acute appendicitis* or *cholecystitis* and operated upon Brucellosis of long duration, with gradual onset fever loss of weight, anemia, hematuria joint pains splenomegaly and even petechiae may be justifiably diagnosed as *subacute bacterial endocarditis* The differentiation is made by blood cultures and skin tests Occasionally the occurrence of orchitis and vesiculitis in brucellosis leads to suspicion of gonorrheal infection

Long enduring cases with nervousness weakness and depression have been mistaken for *neurasthenia*

Prognosis—The mortality rate in undulant fever is from 2 to 3 per cent Infection with the bovine type is usually milder than the porcine infection The average duration is three to four months In about 20 per cent of cases the patient is able to return to work within one month In 25 per cent the period is from one to two months in 35 per cent three to four months in 12 per cent from five to six months and in 8 per cent the period is from six months to two or three years The writer has reported 1 case of incapacity for eight years with ultimate restitution

Prophylaxis—Pasteurization will prevent the cases arising from raw milk Measures for the control of contagious abortion in cattle are reducing the danger from milk but the other great problem of infected hogs has not received attention Apparently the organism penetrates the skin making prevention difficult for veterinarians and abattoir employees Long rubber gloves should be worn by the former when caring for cases of abortion Vaccination with several antigens of the porcine group should be tried on a large scale among slaughterhouse employees Laboratory workers should be vaccinated with several antigens before handling brucella cultures

Treatment—The general measures advocated in the treatment of acute infections are applicable in brucellosis rest in bed forcing fluids alcohol sponges and ice caps as indicated Mild sedatives such as phenobarbital are often necessary and aspirin but not amidopyrine is helpful for aches and joint pains Especial attention should be

Large amounts of thick ropy mucoid material are coughed up swallowed or vomited Perspiration congestion of the neck and scalp veins mental confusion and exhaustion may follow the more severe paroxysms Infants particularly may become so cyanotic and exhausted that they may require artificial respiration

Excitement sudden thermal changes swallowing inhalation of irritating fumes tobacco smoke or even the occurrence of a paroxysm in a nearby patient may excite a spell of coughing If a plug of mucus remains in contact with the hyperesthetic mucous membrane of the respiratory tract recurrent paroxysms very likely follow until it is dislodged Epistaxis often occurs when the spasms are severe Subconjunctival hemorrhages and edema of the lower eyelids occur frequently in cases with severe coughing

Convalescent Stage—The number and severity of the paroxysms gradually decrease vomiting becomes less frequent and the disease thus progresses into the stage of decline or convalescence During this period the hilar and basilar rhonchi gradually disappear For a period of weeks or months an intercurrent infection may cause the major symptoms to reappear even to the point of resembling a new attack

It must be remembered that pertussis is a variable disease and may exist in a very mild atypical form The entire course may last only a few days Proved cases have been known to last but from seven to fourteen days Vomiting and the classical whoop may never occur Very young infants particularly may have choking and cyanotic spells without the whoop

Complications and Sequelae—Bronchopneumonia is by far the most important complication This is usually interstitial in type Lobar pneumonia is rarely seen but occasionally confluent bronchopneumonia produces a lesion which clinically resembles that seen in the lobar type Atelectasis is common due to the blocking of a bronchus with mucus resulting in collapse of a portion of the lung and frequently leading to the erroneous diagnosis of pneumonia Vesicular and interstitial emphysema occurs in practically all severe cases Emphysema of the cellular tissue of the mediastinum may result from rupture of air blebs on the surface of the lung From the mediastinum the air may find its way into the subcutaneous tissues of the neck and even spread to other portions of the body Cases with widespread subcutaneous emphysema are usually fatal In one case of this type which later came to anatomic examination there was hyperleukocytosis of 257 000 Pneumothorax may occur Bronchial asthma and bronchiectasis may result from an attack of pertussis An existing tuberculous lesion may spread during the disease although the effect of pertussis on tuberculosis is probably not as disastrous as was formerly believed Unresolved pneumonia and pulmonary fibrosis are of common occurrence Cardiac dilatation particularly of the right side is observed It is most commonly associated with diffuse pneumonic involvement

Otitis media is frequently encountered and is due to secondary invading organisms Because of the tendency to suppurate the ears require the careful attention of the attending physician

The hemorrhages of pertussis are mechanical in origin resulting from the venous congestion associated with severe coughing Epistaxis and hemorrhage of the bulbar conjunctivae are common Blood tinged sputum is a result of small erosive lesions in the trachea which occur during a paroxysm Hemorrhage of the brain has been reported

The most common neurologic complication of pertussis is convulsions They occur in about 8 per cent of hospitalized cases and are especially common in infants The spinal fluid of those suffering from convulsions is usually normal

Other neurologic complications of pertussis are Epilepsy mental retardation spastic paralysis myelitis and temporary or permanent visual disturbances

Hernia usually umbilical and prolapse of the rectum are results of severe straining associated with the cough Ulcer of the frenum occasionally results when the tongue is repeatedly thrust over the edge of the lower incisor teeth during the paroxysms

Diagnosis—Typical pertussis in the paroxysmal stage can be readily recognized In the catarrhal period and in the atypical abortive form it is difficult to diagnose Pertussis should be suspected in an individual

prevail at intervals of two to four years While cases occur regularly during the summer months, they are more numerous in winter and spring, when complications are likewise more frequent The peak of the incidence in the southern states occurs in May in the North in January or February It appears to be more frequent among females The communicability rate is high resembling that of measles and varicella In family exposures it approximates 85 per cent

Although pertussis occurs at all ages it is decidedly a disease of early life About 85 per cent of all cases occurs in individuals less than seven years of age and about one half of these is found in infants less than two years of age While maternal immunity may be passively conferred upon the newborn in certain instances infants younger than six months of age are very susceptible and are subject to a high mortality

Etiology —*Hemophilus pertussis* discovered by Bordet in 1906 is now considered to be the cause of pertussis for the following reasons

1 The organism is found in the upper respiratory tract during the early stage of the disease but not during recovery

2 The organism is seldom found in normal persons or in those suffering from other types of respiratory infection

3 The disease can be reproduced experimentally by inoculation of the upper respiratory tract of a suitable animal or man with pure cultures of *H pertussis*

4 Specific humoral antibodies may be demonstrated during the course of the disease and after active immunization

Although evidence exists that a filtrable agent may act as a dual etiological factor in the disease it is safe to say that an associated virus is not essential in the reproduction of the experimental disease

Certain other organisms are capable of producing infections of the respiratory tract that closely resemble that produced by *H pertussis* Among these are *Hemophilus influenzae* *Brucella bronchiseptica* and *Bacillus parapertussis* The last two of these probably share common antigen components with *H pertussis*

Pathology —Catarrhal infection of the epithelium of the larynx trachea and bronchi is always present Numerous clumps of *H pertussis* may be demonstrated here The essential lesion probably consists of necrosis of the midzonal and basal portions of the bronchial epithelium with infiltration of this area by polymorphonuclear leukocytes Peribronchiolitis extending from the hilum along the bronchial vascular rays to the middle or even the outer zones of the lung occurs As the lesion progresses typical interstitial pneumonia develops Edema and hemorrhage mark the early stage of parenchymal involvement Accumulation of mucus pus and cellular debris within the alveolar spaces results chiefly from infection by secondary invading organisms It is probable that *H pertussis* is responsible for the lung lesion to a considerable degree

In cases characterized by severe paroxysms or convulsions the brain is intensely congested and may reveal punctate or even large hemorrhages In rare instances encephalitis with degeneration and atrophy of the cortex has been described

Symptoms —The incubation period though variable is usually from seven to fourteen days In a series of 1123 cases Lawson found the mean duration of the period to be thirteen days The course of the typical disease is six weeks in length representing three stages The catarrhal spasmodic and convalescent each lasting approximately two weeks

Catarrhal Stage —This period begins with a mild cough usually nocturnal which progresses in intensity and soon becomes diurnal The mean duration of this period according to Lawson is eleven days Coryza and sneezing are usually present and the appetite fails The cough later resembles that of bronchitis At this stage the physician is frequently consulted In rare instances hoarseness is present and occasionally the disease begins with the features of acute obstructive laryngitis There is often suffusion of the conjunctivae

Spasmodic Stage —After about ten to fourteen days the cough becomes so aggravated that it occurs in series of explosive efforts in which the face becomes congested often cyanotic the tongue protrudes with each cough and the patient appears to strangle Finally the attack ends with a sudden forceful inspiratory crow or whoop

is one of the most fatal The younger the patient the more grave is the prognosis About 60 per cent of the deaths occur during the first year of life In infants under one year the mortality is about 25 per cent during the second year it is about 10 per cent over five years of age the disease is seldom fatal During a period of thirteen years from 1926 to 1939 the mortality rate at the Rochester Municipal Hospital for infants under six months was 30 per cent The Report of U S Public Health Service for the year 1937 recorded 214 652 cases of pertussis from 48 states and the District of Columbia with 4929 deaths a fatality rate of 2 3 per cent In surveyed communities however Sydenstricker and Wheeler have reported the extremely low fatality rate of 0.36 per cent

Prevention—Young infants particularly the debilitated and those with positive tuberculin reactions should be carefully protected from exposure The period of infectivity is about six weeks although the most infective stage is the catarrhal Rigid isolation not only protects others but it shields the patient against superimposed respiratory infections Specific active prophylaxis should be carried out between the ages of six and twelve months The initial course of vaccine should total from fifty to eighty billion organisms The exposed infant should be given immune adult serum hyperimmune human serum or convalescent serum The dosage of these serums should be from 10 to 40 cc injected intramuscularly

Treatment —*General Measures*—Rest in bed is highly desirable Fresh air and sunshine are important but extreme changes of temperature stimulate coughing A range of from 65° to 75° F has been found satisfactory Frequent small feedings are better than large meals If a feeding is lost by vomiting it is well to refeed When abdominal distention is present milk should be temporarily withheld from the diet The use of a snug abdominal support may help If cyanosis is present oxygen is definitely indicated Careful use of suction has been found beneficial in some cases where excessive mucus obstructs the respiratory tract A roentgenograph of the lungs and a cutaneous tuberculin test are recommended during convalescence

Medication—Nearly all sedatives will aid in decreasing the number of coughing spells and help to assure rest and sleep Codeine, paregoric and phenobarbital are commonly used Sodium bromide and antipyrin constitute a useful combination The instillation of a mixture of 2 to 8 cc of ether in 15 cc of olive oil rectally is beneficial if the paroxysms are severe Oversedation is distinctly harmful and causes the patient to retain excessive amounts of mucus in the lower respiratory tract Regan and Tolstoouhov recommended alkalization therapy on the theory that the disease is characterized by a state of uncompensated acidosis



Fig 23—Roentgenograph showing typical bronchopneumonia in a fatal case of pertussis S R., #166171 female 4 weeks of age Third week of pertussis WBC 50 000 Anatomical diagnosis (A—6041) Bronchopneumonia bilateral Bronchitis Pulmonary atelectasis bilateral Bacteriology· Naso-pharyngeal culture H pertussis Hemolytic streptococcus Lungs (Post mortem) *H pertussis*

Specific Therapy—There is at present no evidence that vaccine or other types of antigenic substances possess therapeutic value unless the patient has been previously actively immunized in which case the injection of vaccine during the catarrhal period is indicated

It is important to culture the nasopharynx for secondary invading organisms particularly if pneumonia exists To such cases sulfadiazine 0 1 Gm (1 5 grains) per kg (2 2 lbs) of body weight per 24 hours should be given There is recent evidence that sulfadiazine is also effective against *H*

suffering from a cough of a week s duration if examination of the nose, throat and chest reveals no apparent cause for it History of exposure may not be elicited The physician may be obliged to defer diagnosis until the cough becomes more definite In such instances the patient should be isolated and a culture taken if the facilities are available In doubtful cases inquiry should be made concerning previous injections of vaccine since mild atypical cases may occur as a result of the partial immunity thus conferred

Pathologic Physiology —The essential departures from the normal physiologic state observed in pertussis are (1) those related to disturbances in nutrition (2) those resulting from changes in the pulmonic circulatory system and (3) those referable to the central nervous system

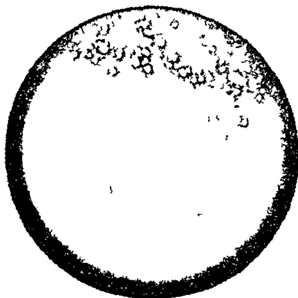


Fig 22 —Photograph of a 72 hour growth of *H pertussis* on Bordet medium Practically pure culture isolated by naso-pharyngeal method

Loss of appetite and vomiting cause weight loss Excessive vomiting may produce gastric tetany In infants diarrhea frequently occurs Dehydration starvation and emaciation impair nutrition to the extent that fatal secondary infections develop

Irritation of the mucous membranes of the trachea and bronchi provokes the paroxysm Obstruction of the lower air passages by mucous plugs induces atelectasis which along with interstitial pneumonia prevents proper oxygenation of the blood According to Regan and Tolstoouhov a state of uncompensated acidosis results Enlargement of the right side of the heart may result from increased impediment of the pulmonary circulation

Anoxemia probably causes convulsions in many instances Infancy, pneumonia and severity of the paroxysms are important factors Cerebral congestion edema, hemorrhage and encephalitis are responsible for convulsive and other types of disturbances in the central nervous system In rachitic infants, convulsions may be due to tetany

The most valuable of the laboratory diagnostic tests consists in the isolation of the organism from the upper respiratory tract This may be accomplished by the cough plate technic or by the nasal swab method Bacteriological diagnosis is particularly applicable during the catarrhal period when positive cultures may be expected in from 70 to 90 per cent of the cases Only positive cultures are significant A single negative culture does not rule out the disease

A characteristic change in the white blood cells occurs during the late catarrhal or early spasmodic stage This consists in a definite leukocytosis of from 15 000 to 40 000 white blood cells per cubic millimeter reflecting progressive increase in the absolute number of lymphocytes Occasionally extreme degrees of hyperleukocytosis occur usually in cases complicated by pneumonia This change in the leukocytes is probably due to direct stimulation of the hematopoietic tissues by *H pertussis* Failure to find this blood change does not constitute conclusive evidence against the existence of the disease

In certain instances the finding of a significant titer of humoral antibodies in an unvaccinated patient may suggest recent infection with *H pertussis* Tests for agglutinins complement fixing and mouse protective antibodies may be made with the patient s serum Unfortunately humoral antibodies do not appear until the paroxysmal stage hence they are of little diagnostic value early in the disease

Attempts to develop a diagnostic skin reaction with various toxins and fractions of the organism have not been entirely successful

Prognosis —In older children pertussis may be a relatively mild disease in infants it

caused by *Pfeifferella whitmori* produces a Straus reaction Although primarily a disease of rodents (rats) in Rangoon Ceylon the Netherland Indies and Indo China at least ninety eight human infections of melioidosis have been reported since 1912 The possibility exists that the causative organism may be found in other parts of the world *Pf whitmori* differs from *Pf mallei* in the following particulars it is motile, forms a corrugated growth attacks a larger range of carbohydrates and decomposes sodium fumarate

Epidemiology —*Equine animals*—In the United States and Canada glanders was quite prevalent until 1905 suppressive measures have almost freed these countries from the disease Complete eradication has been accomplished in Canada and only occasional cases have been disclosed for a good many years in the United States During the World War Germany had to destroy 5776 and France diagnosed 58 843 glanders infections in horses of which 294 died of the disease and 20 585 were slaughtered It is still prevalent in the Balkans (9856 cases in Rumania 1938) and in Russia where as many as 2 to 4 per cent of horses are infected Glanders as a disease of horses mules and donkeys appears in two clinical forms—acute (mules and asses) or chronic glanders of the lung and glanders of the skin and regional lymphatics (farcy) According to Eberbeck who dissected 305 horses the lungs were diseased in 99 67 per cent the region of the nose in 61 9 per cent and the skin in 13 1 per cent of the cases The course of the infection is frequently occult or latent and is recognized only when a mucoid nasal discharge with enlargement of the submaxillary lymph nodes and ulcers in the skin makes its appearance Experience has taught that glanders is spread among equines by water supplies *e g* drinking troughs which have become soiled with the nasal discharge containing the *Pfeifferella mallei* in great numbers Since the bacilli are also excreted from the skin and mouth such objects as feed bags harness brushing and grooming utensils even bedding and fodder liable to contamination with such excretions are especially dangerous By eating of the flesh of glandered horses cats may become infected

Man—Today glanders in man is rare In the Philippines 4 human cases of glanders were seen in 1933 while in the United States 1 case was placed on record in July, 1939 The Bureau of Census records one or two deaths per year The malady affects preeminently those who have intimate relationship with horses suffering from chronic glanders As an occupational infection it is seen in grooms coachmen veterinary surgeons soldiers farmers etc Several cases have been reported in laboratory workers indeed probably no organism with the exception of *Bacterium tularense* is so dangerous to work with as glanders Man to man infections have doubtless been observed in a few instances Infection results most frequently from contamination of an abrasion or wound with glanderous discharge but primary invasion of the conjunctiva and possibly the respiratory and alimentary tract may occur Small epidemics among soldiers and children due to the ingestion of flesh from fallen or killed glandered horses have been reported from Russia

Symptoms —Just as in the horse glanders manifests itself in man in an acute and chronic from In this connection it should be emphasized that chronic glanders frequently may terminate with acute symptoms and in rare instances a case with typical acute onset may run a chronic course

Acute glanders is one of the most dreaded skin infections of man After an incubation time of from a few hours to three weeks on the average four days general malaise anorexia chills fever up to 104° F vomiting diarrhea and rheumatic pains accompany the local swelling and infiltration at the site of the cutaneous infection Ulcers with irregular edges and sloughing yellow grayish bases appear and multiple intramuscular and subcutaneous nodules along the lymphatics the so called farcy buds are gradually transformed into abscesses The skin over these nodes ulcerates the lesions spread rapidly and coalesce into painful serpiginous ulcers with deep sinuses discharging a pink reddish to grayish pus They show little tendency to heal When the infective agent localizes on the mucous membranes (about one third of the acute cases) a papular or pustular eruption precedes the ulcerations When the primary lesions are in the

pertussis Blood transfusions from adult immune donors and the intramuscular injection of 20 to 40 cc of convalescent serum are of therapeutic value *Blood serum obtained* from adults hyperimmunized with pertussis vaccine increases the specific humoral antibodies of the patient when injected intramuscularly in amounts of 20 to 40 cc and constitutes a beneficial form of specific therapy particularly in small infants

If pneumonia exists, it is important to culture the sputum If pneumococci or hemolytic streptococci are present sulfadiazine should be administered

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GLANDERS

(Farcy Morve Rotz Malleus Hautwurm)

Definition—Glanders an infectious disease of equines (horses mules and donkeys) occasionally transmitted to man is caused by a specific micro organism *Pfeifferella mallei* The infection is characterized by the formation of nodular lesions in the internal organs and by ulcerative papules or nodes of the skin and subcutaneous tissues and of the respiratory mucous membrane

History—In ancient times certain diseases of the equine species were known as μηλις Its transmissibility was proved in the eighteenth century its microbic nature was recognized by Chavuveau in 1868 and the *identification of the organism was fully* established by Loffler and Schutz in 1882 and 1886 They isolated the *Bacillus mallei* in pure culture and produced with these cultures typical glanders in horses As a diagnostic agents mallein was produced by Helman in 1891 serological methods were developed by Schnurer (1905) *and the complement* fixation test by Schutz and Schubert (1909)

Etiology—In smears prepared from the viscid pus of the abscesses *Pfeifferella mallei* is seen in extracellular or intracellular location usually in small numbers as straight or slightly curved rods with rounded ends 1.5 to 3.0 microns long and 0.5 micron broad single *sometimes arranged in pairs or* parallel bundles It is nonmotile noncapsulated and gram negative, stains distinctly with alkaline methylene blue or carbolthionin exhibiting a characteristic beaded granular or bipolar appearance The organism produces on all the common culture media under aerobic conditions a slimy growth which has a tendency to develop a brownish coloration with age Particularly on potato media, this pigmentation is readily demonstrable For primary isolation horse serum or potato agar media should be heavily sown with infective material

Since other micro organisms which resemble the glanders bacillus have been described it is advisable to test the pathogenicity of the isolated bacteria on male guinea pigs Following intraperitoneal or even subcutaneous injection the organism localizes in the serosa covering the tunica vaginalis and incites a thick purulent exudate The testes are swollen (second to *twelfth day) and the scrotal skin may* become adherent and ulcerated the animal usually dies between the tenth and the fourteenth day This testicular reaction first described by I Straus (1889) is diagnostically significant provided the exudate *is* controlled both microscopically and culturally Several different species of bacteria (*B pyocyaneus B preisz nocard Brucella* etc) and fungi (*Sporotrichum Coccidiomyces* and others) produce a Straus reaction similar to that induced by *Pfeifferella mallei* Of particular importance is the fact that the organism of *melioidosis* a disease of man which resembles glanders very closely and is

ease is diagnosed Very few cases ever recover On the other hand the curability of chronic glanders is recognized and according to various authorities from 30 to 50 per cent survive independently of treatment

Treatment—The patient must be isolated and the discharges carefully disinfected Aside from symptomatic treatment and complete rest most of those who have had experience with glanders are convinced that drugs have no effect on the disease Prompt and radical surgical measures are the most reliable means of treating the chronic disease Vaccine therapy has been tried with some success in a few cases (Gaiger Zieler and O Fischer) Chemotherapy with diverse preparations (mercurial inunctions copper derivatives and arsenicals) has yielded no success

Prevention—The prevention of glanders in man depends on the vigorous suppression and ultimate eradication of the disease in horses Until accurate diagnostic methods had been worked out the control of glanders was difficult since mild abortive and latent glanders are common and important factors in the spread of the infection in the crowded parts of cities With the aid of the mallein test—intradermal palpebral and ophthalmic—and the agglutination complement fixation and conglutination tests horses in infected or suspected stables are now accurately examined All animals proved to be infected with the disease whether in the clinical or latent form must be destroyed and properly disposed of and the stable and objects exposed to contamination thoroughly cleansed and disinfected with bleaching powder preparations Horses which have been in contact with infected animals although considered healthy by allergic and serologic tests must be reexamined every three weeks Should there be no indication of the disease in these tests the stable may be considered free from glanders The education of persons who handle horses should call attention to the importance of rubber gloves thorough disinfections and other methods of protection Special care should be taken to prevent the spread of the disease through the discharges and contaminated fomites from human cases Cultures of *Pfeifferella mallei* and laboratory tests with the organism are dangerous and should not be entrusted to beginners

KARL F MEYER

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ANTHRAX

(Charbon Maladie Charbonneuse Milzbrand Malignant Pustule or Cutaneous Anthrax Woolsorters Disease Rag Pickers Disease or Pulmonary Anthrax)

Definition.—An acute infectious disease—caused by the *Bacillus anthracis*—which attacks many species of animals in particular herbivora and is transmissible from them to man Clinically it takes the form of an external (malignant pustule and malignant edema) or internal (pulmonary and rarely intestinal) disease

Historical—Anthrax as a disease has been known from antiquity the name is derived from the Latin *Anthrax* a carbuncle Maret (1752) and Fournier (1768) defined the clinical type of malignant pustule in man while Chabert (1780) described anthrax in animals and Barthelémy (1823) proved its transmissibility by inoculation Subsequently Davaine (1863–1864) showed that anthrax was caused by a living organism that multiplied in the body invaded the blood stream and produced death by septicemia He found the same organism in the malignant pustule and thus demonstrated the etiologic identity of the disease in man and animals The final proof of the causative role of *Bacillus anthracis* was furnished by R Koch (1877) in his classic monograph when he described the formation of spores the cultivation of the organism in vitro the reproduction of the disease by injection of pure cultures and the recovery of the bacillus at autopsy Thus the study of anthrax established for the first time the specific relationship of a microbe to an infectious disease

Etiology.—The *Bacillus anthracis* so designated by Ferdinand Cohn (1875) and by many claimed as the corner stone in modern bacteriology in a non motile gram positive rod which forms capsules in the tissues of man and animals and sometimes

nose the sticky blood tinged secretion gradually becomes converted into ropy, viscid mucopus and excoriates the skin over which it runs, forming crusts on the lips and mouth Sometimes the disease commences with symptoms suggesting influenza, pneumonia or typhoid fever, one is then struck by the degree of prostration, which is entirely out of proportion to the clinical signs With the development of localized purulent foci a bacteriologic examination may establish the exact nature of the infection An *exanthematic eruption* in the form of brawny, purplish lentil shaped spots and pustules containing clear yellow white matter, which appear on the face neck, trunk and limbs is indicative of sepsis and is the precursor to death Invariably the glanders bacillus may be isolated in blood cultures Delirium and coma precede the fatal termination which may occur within one to seven weeks, due to circulatory collapse

Chronic glanders may at first show negligible constitutional symptoms, fever may be absent although general malaise inertia and pains in the extremities are comparatively common Within one to four weeks however an irregular fever develops which tends to assume a septic character with deep remissions The most constant lesions make their appearance in the form of subcutaneous or intramuscular abscesses or tumors on the upper and lower extremities on the head and neck, rarely on the trunk as a rule the regional lymph nodes are enlarged The earlier lesions are usually very painful and tender, they may rapidly ulcerate or on incision suppurate profusely, discharging specific organisms in small numbers Stubborn resistance to treatment and partial healing with discharging sinuses and a tendency to spread are striking features of the disease Involvement of the joints and periosteum of the bones is not rare Pulmonary and pleural disturbances in the form of bronchitis consolidation and exudates are reported in about one quarter of the cases Some cases present only the symptoms of a minor ailment but lose rapidly in weight and strength Emaciation usually accompanies the development of foci Periods of irregular fever and profuse sweating may be followed by quiescent intervals during which the patient may regain his strength

This peculiar remittent type of disease may drag on for years the average duration from a minimum of six weeks to a maximum of fifteen years is about one and one half years Remissions at intervals of from two to five years have been observed The lesions may heal slowly, or a remission with rapid generalization resembling acute glanders may lead to a fatal termination Many cases succumb to cachexia and amyloid disease Chronic glanders may be latent at the beginning and during the entire course of the disease A personal account of chronic relapsing glanders in a veterinarian gives a vivid description of this distressing malady (Gaiger)

Diagnosis—The varied clinical picture renders the diagnosis difficult However, any wound infection in a person with a history of contact with glandered horses or with laboratory handling of *Pfeifferella mallei* should be regarded as gravely suspicious and proper bacteriologic tests by culture and animal inoculation should be instituted Aside from the bacteriological tests the *newer serologic procedures* are indispensable The most trustworthy reactions have been obtained with the complement fixation test the technic is the same as that used in the recognition of latent equine glanders As a rule the serum of a patient with glanders fixes complement in a dilution of 0 1 to 0 05 cc Agglutination reactions in dilutions of 1 800 are diagnostic In chronic glanders the antibodies persist for a long time but certain fluctuations in titer have been observed It is therefore advisable to employ several methods of examination (complement fixation agglutination and conglutination) and to make repeated tests The allergic tests with mallein are rarely used although the ophthalmic and cutaneous tests are always positive in glandered human beings In fact the injection of dead *Pfeifferella mallei* for therapeutic purposes induces both local and general reactions The glanders like disease *melioidosis* described by Stanton and Fletscher is not readily diagnosed or differentiated from glanders during life At autopsy the causative organism can be readily isolated from the visceral lesions

Prognosis—The gravest prognosis must be rendered when the acute form of the dis

to 3 per cent) have occasionally been recorded the disease may take the form of anthrax meningitis The carelessness or indifference of manufacturers in using Chinese Indian or Siberian horsehair due to upsetting of the usual trade routes was largely responsible for these infections

The second type which may take the form of cutaneous anthrax or of pulmonary disease is dependent on an infection acquired during the treatment of animal products It shows no seasonal incidence Of the 262 cases reported in the United States between 1934 and 1938 skins hides and tanneries were responsible for 93 wool 38 hair and furs 18 while 89 occurred among agricultural workers (Henry Field Smyth 1939 Sixth Report of the Committee on Anthrax) The products—hides and hair—soiled with blood invariably come from regions where the disease in common in animals and the civilization low Pulmonary infection was commoner than malignant pustule fifty years ago but thanks to improvement in industrial hygiene legislation and the introduction of exhaust ventilation dust masks proper clothing etc this type is now infrequently seen and reported

The statistical data collected by the United States Public Health Service and supplemented by the analyses made by Henry F Smyth are listed below and indicate that approximately 60 to 80 cases of anthrax with a case fatality rate of from 17 to 22 per cent are recognized annually in the United States (principally Pennsylvania New York Massachusetts and Texas)

Years	Cases	Deaths
1919–1923	461	107 (23%)
1924–1928	468	100 (20%)
1929–1933	379	85 (22%)
1934–1938	375	61 (16%)

The infection chain—animal man—is invariably broken no instance is known in which the disease was conveyed from man to man although a healthy person may be a carrier (passive porter) as regards spores in his clothing

Symptomatology —(*A*) *External Anthrax* —1 MALIGNANT PUSTULE —The most common form (95 per cent) of cutaneous anthrax is seen by the physician when the carbuncle has already developed From one to three days after the infection the reddened area of the skin on the arm neck or face shows a fleabite like patch which is transformed into a painless and insensible papule Intense itching accompanies this primary lesion in its evolution to a vesicle with a hard dark purplish black center It is of interest to note that the site of the lesions varies with the nature of the industry Hide porters are frequently infected on the back of the neck which is more open than other parts to excoriation In the case of butchers and veterinarians who handle carcasses the arms or hands are affected As a rule only one focus is present although the scratching may lead to auto-infection and the formation of several papules and multiple vesiculation with yellowish or hemorrhagic or even purulent content Within a few hours after the appearance of the papules the soft tissues in the immediate vicinity become infiltrated and swollen Coagulation necrosis desiccation or scratching by the patient produces a dark bluish red tough leathery eschar which extends both with regards to depth and width and forms with the densely edematous ring studded with small vesicles the characteristic carbuncle The term pustule is unfortunate for pus formation is absent The massive infiltration joins an extensive hemorrhagic edema which may extend along the neck to the face or chest or even to the abdomen and lead to extraordinary distortion of the involved parts Reddened lymphatics spread from the carbuncle to the regional lymph nodes which are painful swollen and sometimes covered by an area of reddened and inflamed skin In the mildest form with but little swelling the primary papule vesiculates rapidly and the resulting scab separates in a few days Recovery in the more severe cases is indicated by the gradually sloughing suppuration of the eschar at the end of the first week recession of the edema and slow healing of the extensive defect by granulation leaving a disfiguring scar

Quite early general symptoms in the form of headache joint pains nausea malaise and fever may accompany the evolution of the carbuncle The temperature varies in the majority of cases it is elevated on occasions it may be normal or even subnormal The count of the white blood cells may show a slight increase (10 000–13 000) or a

on artificial media, grows on agar in characteristically long (up to 10 microns), segmented parallel or interwoven chains Under conditions of unfavorable growth outside the body it forms ellipsoidal or oval spores which are quite resistant to heat (ten minutes boiling) and to chemical disinfectants like $HgCl_2$ which they resist for seventy hours in concentrations of 1 1000, but are readily destroyed with agents acting by oxidation Potassium permanganate in 4 per cent solution kills in fifteen minutes or hydrogen peroxide in one hour The capsule consisting of a glycoprotein is definitely correlated with the pathogenicity of the bacillus for a diversity of animals besides the herbivora and man Infections of guinea pigs and mice may best be achieved by the intramuscular route of relatively large doses of bacilli In culture the organism produces *toxic albumoses* largely disintegration products of proteins in the media When freshly isolated from the animal body, the anthrax bacillus rarely causes difficulty in identification The capsule formation the inverted fir tree growth in gelatin stab and the pathogenicity for guinea pigs distinguish the microbe from those of anthrax like or pseudo-anthrax bacilli (*B subtilis* and *B megatherium*)

Epidemiology—As a disease of *animals* with a worldwide distribution anthrax has been known for centuries The character of the infection chain is fairly clear and it is fully established that man contracts anthrax secondarily through direct or indirect contact with animals or animal products Rarely is anthrax spread from animal to animal, infection occurs primarily and secondarily by the alimentary tract from feeding on contaminated pasture in lowlying marshy areas stagnant pools or banks of rivers where in warm countries the bacillus may grow during the summer months In cold countries the sources of infection are artificial food stuffs such as bone blood fish maize meal and oil cake A mechanical transmission by biting flies occurs infrequently Anthrax in animals (cattle, horses sheep goats buffaloes elephants and minks) takes the form of a septicemia varying from an acute apoplectic attack to a subacute disease accompanied by intestinal disturbances local cutaneous swellings and a mortality of from 75 to 100 per cent In dogs cats, and swine the disease results from feeding on the carcasses of infected cattle the localization is principally in the larynx and pharynx and may be mild or latent The bacilli in the blood or discharges are in the vegetative stage but rapidly sporulate when exposed to suitable temperatures and oxygen These spores are very resistant Multiplication in the soil depends on the hydrometeorologic condition they remain viable in the soil for over fifteen years (Pasteur)

Distribution and Incidence—Anthrax infection is known to exist in a few fairly well defined districts in the United States these are (1) southeastern South Dakota and northeastern Nebraska, (2) the delta regions of the lower Mississippi Valley and (3) a belt along the Texas gulf coast In these districts occasional serious outbreaks occur but the incidence is kept down by appropriate preventive measures

Anthrax in man may be conveniently divided into (1) the *nonindustrial type* (11 16 per cent), affecting farmers butchers sheepherders veterinarians and others who come in close contact with diseased or fallen animals or insect bites and (2) the *industrial type* arising from the handling of hides and skins (37–46 per cent) or wool animal hair and bristles (28–34 per cent) and occurring in the hide tanning and leather industries brush and broom making horse-hair factories furriers and taxidermists rag sorting horn and grain porterage The susceptibility of man to anthrax is relatively low and individually quite variable it may be enhanced by chronic systemic diseases such as diabetes The first type also described as *agricultural anthrax* which takes the form of malignant pustule is due to contamination of the skin with material from infected animals rarely the bites of insects (Louisiana seven cases) It is quite seasonal the incidence depending on the extent of anthrax in the animals The ingestion of infected food such as sausage or the improperly cooked meat of anthrax animals may give rise to the intestinal form of the disease (Gipsies South African natives) milk is seldom involved since the cow sick with anthrax is removed Infection by ingestion is quite rare in the United States Cases of anthrax from *shaving brushes* (0 08

patients showed no objective symptoms they were restless and revealed in their facial expressions great anxiety and concern for their health Collapse cyanosis and apo plectic death terminated the infection of the majority within one to three days, in one case the course was prolonged for eleven days At autopsy localized phlegmonous hemorrhagic infiltrations and carbuncles were noted in the ileum and cecum and hemorrhages in the myocardium and brain

Diagnosis —The diagnosis of anthrax is greatly facilitated when the cutaneous lesions are characteristic and when the an amnesis and occupation of the patient sug gest the nature of the infection In case no information is available the differential di agnosis between an anthrax carbuncle and a simple coccal infection requires laboratory assistance Any physician possessing a micro scope of medium power and some staining reagents can make an early diagnosis and thus reduce the risks attending the disease If a vesicle has formed films are made from the serum and stained If it is already broken gentle scraping of the pimple or puncture of the eschar will produce serum rich *in typical encapsulated bacilli when* stained with a polychrome eosin methylene blue stain (Wright or Giemsa) Their di rect cultivation on peptone agar should al ways be attempted In case the specimen has to be shipped the tissue serum should be dried on silk threads or a sterile glass slide On occasion both the smear and cul ture may show anthrax bacilli in small num bers or even none at all while several varieties of cocci may grow in the culture Re peated examinations and cultures are therefore indicated In view of the occurrence of anthrax like bacilli on the skin it is impera tive that all anthrax diagnoses should be confirmed by animal inoculations preferably on guinea pigs or mice In pulmonary an thrax the bacillus has been found micro scopically in the sputum and in the pleural exudate The vomitus should be inspected when gastro intestinal anthrax is suspected

During the terminal stages of the disease and sometimes when severe general symp toms are present the bacillus may be cul tivated from the blood stream if not less than 20 cc of blood are taken Even in non fatal cases and in the absence of symptoms indicative of generalization the anthrax ba cillus may be isolated from the blood stream Blood or spinal fluid, after it has been treated with 3 per cent acetic acid solution may be centrifugalized and the sediment ex amined with a Wright s stain for bacilli Estimation of the phagocytic power of the leukocytes in the hands of an expert may be of diagnostic and prognostic importance

Prognosis —It is quite generally recog nized that the prognosis in external cuta neous anthrax is favorable provided the pustule is not on the neck or face and has not been irritated by physical and chemical procedures Moreover, if the nature of the pustule is correctly and promptly diagnosed the patient placed in bed and specific treat ment is instituted not later than the third day the chances for recovery in the great majority of infections are favorable To be sure the statistics amply attest to the event ful recovery without complications or se quelae without specific treatment On ac count of the variable individual disposition of man to anthrax it is doubtless true that cutaneous even visceral infections are not as deadly as popular belief would indicate *Thompson reports on the anthrax infections* of veterinarians only one of the twenty cases (eighteen with malignant pustule one throat infection and one generalized) ended fatally However it is well to remem ber that the general fatality rate is around 20 per cent (Holland and U S A) but may be as high as 40 per cent There is generally a low fatality rate for tannery anthrax but a high rate for the form that results from animal contact Septicemia with and with out involvement of the viscera and some times meningitis are serious complications In fact double and multiple infections occur at times and recurrences are possible though not usual When the eruption assumes the form of anthrax edema indications of di minished resistance are obvious and the out come may be in doubt In respiratory and *alimentary anthrax the prognosis is grave* largely on account of the extensive visceral destruction and the presence of a bacteremia (up to 300–400 bacilli per 1 cc) The pres ence of bacilli in the blood culture justifies an unfavorable prognosis although by mod ern therapeutic procedures such as specific serum dramatic cures may be achieved

leukopenia with 60 to 85 per cent polymorphonuclear leukocytes Despite the alarming aspect of the carbuncle the general manifestations of illness may be exceedingly slight On the other hand even the early stages of the local process may be accompanied by profound malaise, vomiting, circulatory collapse, cyanosis, profuse perspiration diarrhea and subnormal temperatures Death may take place in from three to five days Blood cultures usually reveal anthrax bacilli

The presence of bacilli in the blood stream does not always constitute an unfavorable prognosis In fact the mode of action of the anthrax bacilli is by no means clearly understood The invasion in the blood stream occurs late remains confined to the blood vessels of the liver lung spleen and kidney and is accompanied by severe toxic manifestations

It is not unlikely that embolic bacillary occlusions of the capillaries and the formation of poisons in the extravasations of blood into the organs are principally responsible for the severe symptoms and deaths According to Szendey, cerebral hemorrhage is present in at least 40 per cent of the fatal cases Cyanosis and respiratory distress are always grave symptoms

2 Malignant anthrax edema is observed in the loose connective tissue of the eyelid hand neck thigh and mucous membranes It is characterized by a doughy soft transparent faintly reddish or anemic infiltration and swelling without papules and vesicles following rather than preceding constitutional symptoms Rarely circumscribed it spreads rapidly and is apt to terminate in extensive sloughing and gangrene In general the outcome of the edematous form is less favorable than that of the carbuncle

(*B*) *Internal Anthrax*—3 Pulmonary anthrax presents no characteristic clinical symptoms The onset is sudden with rigor and fever which may be slight or excessive Aside from general *malaise* headache and circulatory disturbance the patients may complain of a feeling of tightness in the chest and difficulty in breathing which in some may be accelerated to the extent of 40 to 50 respirations to the minute The sensorium is mostly clear The auscultating signs are usually those of a bronchitis An examination of *the nose larynx and pharynx* discloses reddening and swelling of the mucosa With increasing dyspnea, cough and pain in the chest pneumonic infiltration or even pleuritic exudates, becomes discernible, In the frothy, occasionally blood tinged sputum, anthrax bacilli may be demonstrated Death may occur within eighteen to forty eight hours, when the disease is of longer duration (up to ten days) delirium and unconsciousness govern the clinical picture On the other hand, absence of the severe symptoms usually accompanying acute infections and the rapidity with which collapse sets in are characteristic features of this form of anthrax *Not infrequently*, *the disease* is suspected on account of the occupation which subjects the patient to inhalation of dust from hairs soiled with spores Massive doses of serum should then be administered without awaiting the bacteriologic diagnosis since without treatment the mortality is nearly 99 per cent McKitterick and Pearson report as a complication the damaged vision in a two and one half year-old child with pulmonary anthrax

4 Gastro intestinal Anthrax—This form which is rare in the United States may result from the ingestion of infected food or may follow the external type when the organisms are carried to the mouth from the external lesions it may occur as a secondary manifestation of anthrax in some other part of the body Sinai calls attention to instances of symptomless infections in a group of people who ate partly cooked meat from a calf which had succumbed to anthrax The sera of fifteen of thirty eight persons who had ingested the meat gave positive precipitin reactions with a specific anthrax serum In an epidemic due to sausages involving thirty people Solowieff (1930) noted the following symptoms in the cases which he subsequently autopsied persistent vomiting constipation rarely diarrhea the intestinal tube was usually empty and occasionally blood tinged fecal material or pure blood was discharged The abdomen was distended and tender and since a peritonitis was always present accumulations of exudate were usually discernible The temperature usually remained normal rarely exceeded 102 2° F and following profuse perspiration dropped to normal Although the

arsenicals to antianthrax serum on account of the risk of serum sickness in veterinarians (Thompson 1937) Gilbert treated nine cases with novarsenobenzene and only two infections ended fatally while among untreated patients the mortality is said to be nearly 100 per cent in African natives The serum treatment remains however, the method of choice and is doubtless the only therapeutic procedure which may be employed with any degree of hope in the generalized visceral forms of anthrax Of seven cases with generalized infection Sabolotnyi treated four with serums with three recoveries while three were not treated and all died Sulfapyridine sulfathiazole sulfadiazine and sulfanilamide in the order named have been used by Gold in the treatment of forty two cases of anthrax with excellent results in thirty nine The drug of choice is sulfathiazole in large doses If the edema is not controlled by the third day large doses of antianthrax serum must be given In the treatment of anthrax preference is now given chemotherapy with sulfonamide compounds

Prevention —The prevention of the disease in man must first be directed to a suppression of the infection in animals by veterinary control measures disinfection of all raw materials in which horsehairs hides wool and other substances are liable to harbor the anthrax spore The sick animals must be isolated or killed and carcasses must be promptly disposed of by burial with lime (at least three feet deep) or by burning without skinning Vaccination of the live stock with carbozoo —a spore vaccine containing 2 per cent saponin (Mazzuchi and Hruska)—is being employed with considerable success The disinfection of the hair and wool from anthrax infected or suspected areas may be done by boiling for three hours or with steam under pressure Hides and skins are treated in a hydrochloric acid and salt mixture at 40° C for six hours Workers in tanneries and wool factories may be protected by rubber gloves and aprons and by proper ventilation to carry off the dust. Active immunization of workers exposed to goat hair imported from China with a heat killed anthrax vaccine has been tried by Gold but two cases so vaccinated were not protected

KARL F MEYER



Fig 25 —Same patient after intravenous serum therapy

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Some writers claim a recovery rate of 10 per cent or more, but in many of these cases a bacteriologic diagnosis was not made The true nature of mild cases may occasionally be suspected but is rarely proved An attack of the disease, if it produces immunity induces a resistance of only short duration Second attacks of cutaneous anthrax have been known to occur within a year

The average hospital stay is about two weeks and provided the ulcer heals in two weeks, the patient returns to work within five to six weeks

Treatment—In recent years the treatment *of anthrax in man has* been placed on a sound foundation and many of the traditional procedures and conceptions have been abandoned Few authors still recommend incision excision or cauterization of the carbuncle or other meddlesome local manipulations except in diabetic patients (Rodriguez Villegas) Almost all reports stress the need for absolute rest of the patient in bed and immobilization of the affected part As local antiseptic dressings mercury bichloride (1 2000) potassium permanganate (1 1000), borated petrolatum or ichthyol are recommended

The use of the *specific antianthrax serum* first introduced by Scalvo (1895–1896) and administered intravenously or intramuscularly is now universally recommended as a dependable treatment of external or internal anthrax The early administration of a large dose of serum is an essential part of the treatment In the writer s experience 300 to 600 cc serum diluted with 10 to 15 per cent glucose solution and infused intravenously lead in most cases to a disappearance of the edema, general malaise and headache, and a return to normal temperature and pulse The serum may be given in one, two or three large doses The first dose *of serum should not be less than 150 to* 300 cc Repeated small doses rarely are as effective as two or three large doses except *in the infections with* bacteremia when daily two to four injections of from 40 to 50 cc of serum are given Nilson saved a case of anthrax bacteremia by treating it with 13 400 cc of serum of which 7600 cc were given intravenously There is no necessity to give serum until the lymphadenopathy has receded Local administration of serum around the carbuncle is contraindicated in fact in some cases decidedly harmful In the series of cutaneous anthrax cases treated by Legge Hodgson Gold and others the mortality was reduced in 7 per cent According to Smyth the case fatality rate of 312 cases treated with serum was 30 or 9 per cent The way in which the serum acts is unknown it is supposed to contain opsonins

More and more combination treatments with arsenicals and serums are coming into favor The method of choice is apparently 2 to 3 injections of 0 6 to 0 9 Gm *of neo*arsphenamine on the first and second day after the injection of the specific serum Eurich (1933) has had a mortal*ity of* only 5 per cent in his last 200 cases of cutaneous anthrax so treated If serum is not available, neoarsphenamine in *dosage of* 0 75 Gm three times a day every three to five days may be tried In 27 cases so treated no deaths were *reported* Danish workers prefer



Fig 94—Cutaneous anthrax in a butcher before serum treatment.

Lepus) No human infections have been traced to domestic rabbits, although spontaneous disease has been observed in these species The infective agent enters through wounds or through the unbroken skin (2) *Bites of insects* of determined species (ticks and *Stomoxys*) and of undetermined species (mosquitoes and fleas?) are responsible for many cases The deer fly (*Chrysops discalis*) is the principal source in Utah (Hillman and Morgan), the wood tick (*Dermacentor andersoni*) and dog tick (*Dermacentor variabilis*) cause infections in the western and southern states (3) *Bites* of such animals as cats opossums coyotes dogs skunks squirrels hogs muskrats raccoons lambs etc have been followed by tularemia (4) *Contact with sheep* (in particular with the ticks and their fecal droplets in the wool of sheep) is responsible for occupational infections in sheep shearers (5) *Skinning and dressing of mammals* [tree squirrels coyotes skunks deer muskrats foxes and water rats in Russia (*Arvicola amphibius*) birds (quails sage hens chickens) and cold blooded animals (bull snakes fish baited with rabbit meat)] (6) *Laboratory infections* are observed so frequently (at least 60 are known) that some writers have expressed the opinion that every one who works with infected animals will ultimately contract the disease The mode of transmission is obscure Russian workers suspect the aerogenic pathway because the wearing of a face mask apparently prevents this infection

B tularense requires no particular portal of entry for its penetration It is not surprising consequently that in addition to contact infections tularemia has been caused by the *ingestion* of partially cooked rabbit meat (twenty cases with twelve deaths Amoss and Sprunt) and by the drinking of water from a brook contaminated by water rats (43 cases in Russia Karpoff and Antonoff 1935) The contagiosity of the infection is very low No proven human case to case transmission has been reported an increasing incidence of pulmonic tularemia however suggests the possibility of a transmission by way of the sputum Multiple familial infections by handling the same rabbit have been reported by Kavanaugh

Ecology of the Reservoirs—The key factors in the transmission of tularemia are ticks and wild rodents (representatives of the Leporidae, Sciuridae and Muridae) For its propagation in nature *B tularense* depends entirely on the wood ticks *Dermacentor andersoni* Stiles, and the dog ticks *Dermacentor variabilis* and *occidentalis* which feed on rabbits and other rodents A hereditary transmission through the eggs of the tick to the larvae and nymphae maintains the well regulated organization of the chain of infection This problem of the multiple factors involving the bionomics and ecology of insects and rodents varies from region to region and from country to country and thus creates a complex kaleidoscopic epidemiologic picture which thus far has been sketched only in its broader outlines

Morbid Anatomy.—The autopsy reports (56) placed on record by Foshay, Lillie and Francis stress in both the acute and subacute stages of the disease focal areas of necrosis throughout the body in various phases of evolution Macroscopically whitish yellow foci ranging in size from those hardly visible to the eye to those measuring 8 cm in diameter are found in the lymph nodes spleen liver kidneys and in a certain percentage of the cases in the lung Necrobiotic processes consisting of nuclear fragmentation and infiltrations with polyblasts in the early stages are replaced later by a central area of detritus cuffed by monocytes and fibroblasts in a fairly characteristic radial arrangement and peripherally encircled by lymphocytes and an occasional cell of the Langerhans type Pulmonary tularemia is characterized by grayish white necrotic foci surrounded by hyperemia and extravasation which extend from the pleura into the parenchyma of the lung

Symptoms—The period of incubation in tularemia is from one to ten days according to Francis it does not exceed five days the average being three and one tenth days while Kavanaugh places it at four and one half days Only the typhoid type proceeds as a general disease without local processes Since the *onset* is sudden the patient usually remembers not only the day but the hour at which he fell ill Severe headache vomiting chills and fever with an initial rise in temperature above 104° F accom

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TULAREMIA

(Plague like Disease of Rodents Deer Fly Fever Tick Fever, Rabbit Fever)

Definition —Tularemia is a specific infectious disease caused by *Bacterium tularense* It is a potent factor in the destruction of wild animal populations acting as a heterogeneous infection chain with a broad spectrum of infection in which a great variety of rodents and insects participate as reservoirs and vectors Man may enter into the chain accidentally or occupationally by contaminating his hands conjunctival sac or buccal cavity with the infected internal organs and body fluid of mammals birds and insects, or by the bite of an infected blood sucking fly or tick Wild rabbits and hares have been the principal sources for the disease in man

History —Tularemia is not a new disease without a doubt having existed unrecognized for a long time It is proudly called a truly American disease because of its discovery in America (California) and because Americans contributed the basic knowledge concerning it McCoy in the course of his studies on plague in 1910 discovered a disease among ground squirrels (*Citellus beecheyi*) characterized by pathologic lesions similar to those of plague This plague like disease of rodents was encountered in rodents shot or found dead in Tulare County California When McCoy in cooperation with Chapin succeeded in isolating the causative organism he named it *B tularense* Shortly thereafter Wherry established bacteriologically the first infection in a human being and recognized the hare as an important reservoir of the disease Francis in 1919 and 1920 investigated rabbit fever in Utah and discovered that the blood of a rancher who had been bitten on the neck by a deer fly and had died on the twenty sixth day of his illness produced in the guinea pig the plague like disease described by McCoy In rapid succession he reported the discovery of *B tularense* in jack rabbits the experimental transmission of the disease by the bite of the deer fly (*Chrysops discalis*) and the rabbit louse (*Haemodipsus ventricosus*) the cultivation of the organism on new media and the serological diagnosis The role of ticks as important reservoirs and vectors of tularemia has been elucidated by Parker and Spencer (1926 and 1929) and by Green (1929)

Bacteriology —*B tularense* is a sho[rt] gram negative rod pleomorphic forms a[re] coccoid, occasionally bipolar but nonsporin[g] It is capsulated and according to Ohara slightly motile In smears it is gram neg[a]tive but stains well with fuchsin or cryst[al] violet, while in sections it is not demo[n]strable with certainty *B tularense* is an i[n]tracytoplasmic parasite with great affin[ity] to ectodermal epithelial cells (Buddingh a[nd] Womack 1941) Under aerobic conditio[ns] it grows well only on gelatinized hen s egg yolk and rabbit blood glucose cystine or thioglycolate agar Heating at 58° C for 10 minutes or cooking kills the organisms The usual disinfectants, for example 1 0 per cent tricresol, destroy the bacteria in two minutes It remains viable in pure neutral glycerin at —14° C for two years Preservation at —76° C is likewise effective for months The guinea pig is used for laboratory tests and the mouse for testing specimens of sputum

Epidemiology and Ecology of the Reservoirs —Tularemia as an endemic disease of man (over 10 118 cases known) has been observed in forty six states and the District of Columbia of the United States and Alaska it has been reported from Canada Japan the Soviet Union and in recent years in epidemic proportions from Europe (Sweden Norway Bohemia Austria Turkey Germany) Cases of natural infection occur in every month of the year but they are most prevalent in summer time in the western states where ticks (March to August) and deer flies (June to September) are the cause of infection or when jack rabbits are being dissected (April to October) in the eastern states when East of the Mississippi River Game Laws permit the hunting of cotton tail rabbits (November to January) The highest annual incidence on record is that of 261 cases in 1939 Men and women of all races and all ages are equally susceptible to the disease

According to Francis at least twenty methods by which man may be infected with tularemia are known The most important sources of infection are (1) Over 90 per cent of the human cases in the United States are traceable to contact with infected *rabbits* (cotton tail rabbit *Sylvilagus floridanus* jack rabbit and snowshoe hare

or may develop on a hematogenous basis secondary to some primary focus on the skin or elsewhere In the first group pulmonary symptoms less abrupt than in the pneumococcic types initiate the disease hacking non productive cough dyspnea fever malaise and occasional chills are present Pleuritic pains may be a dominating symptom Cases of milder involvement appear as atypical pneumonias in which the pulmonary lesions may last for a month One laboratory infection probably caused by the aspiration of bacteria from an incompletely killed suspension of *B tularense* was tentatively diagnosed as psittacosis until the specific bacterium was isolated from mice inoculated with the sputum Primary pneumonic tularemia is not well known but according to recent reports the incidence throughout the country is strikingly on the increase In another large group of cases pulmonary tularemia develops in patients having well recognized tularemia with ulcers or infections of the eye Cases of this type offer no problem in diagnosis as a rule the sickest patients are most likely to have involvement of the lungs Pleuritis usually is present and the development of a pale yellow slightly cloudy pleural effusion of high specific gravity but low cellular count (2000 to 5000 per cubic millimeter) is of great diagnostic value The pneumonic consolidation as parenchymal confluent or lobular bronchopneumonic infiltration consists of small patchy later large coalescing areas The physical signs may vary from day to day indicative of a migratory type of pneumonia usually more extensive in one lung than in the other When the process is predominantly necrotizing in character gangrene cavitation and pulmonic abscesses develop in those cases in which the disease is most severe Despite large cavities or abscesses the sputum is moderate in amount, mucopurulent and rarely blood tinged or rusty X ray films taken from a few days to two weeks after onset may reveal a slowly advancing lobular type of consolidation The mediastinal and peribronchial lymph nodes almost always are enlarged

Oral and Abdominal Tularemia—Ingestion of insufficiently cooked wild rabbit meat or water contaminated with *B tularense* may cause a violent local process in the form of a necrotizing pharyngitis or angina abscesses on the roof of the mouth ulcers in the pharynx and nasopharynx fever enlargement of the submaxillary and anterior cervical lymph nodes and, in some cases conjunctivitis Vomiting excruciating pains in the abdominal regions and diarrhea begin either during the febrile period or after the temperature has fallen The course may be fulminant children have developed convulsions become stuporous and died in the first week of illness In adults there may be enlargement of the regional lymph nodes accompanied by fever but no deaths have been reported Russian observers have reported the persistence of enlarged submaxillary lymph nodes up to eight months after infection

Complications—Symptoms of general peritonitis with the finding of plastic exudate at autopsy (Francis Fulmer) and persistent ascites requiring tapping three and five months after onset have been reported Appendicitis diarrhea and intestinal hemorrhages may be present during the last days of illness Occasionally pericarditis pneumothorax thrombosis of the veins or osteomyelitis complicate the convalescence Meningeal or leptomeningeal localization demonstrated by the isolation of *B tularense* from the spinal fluid usually is fatal Diffuse encephalitis in acute tularemia has been observed at autopsy by Hartman

Convalescence and Prognosis—Many of the patients are ambulatory In about one-third of the cases recovery even without complications is slow but *confers a permanent* immunity According to Foshay the mean duration of fever is twenty six days the duration of the adenopathy from three to four months and the duration of the disease five and one half months Even though clinical recovery is evident the *B tularense* because of its facultative intracellular parasitism may remain alive in the tissue for months and perhaps years (Blackford Foshay and Mayer) Pulmonary tularemia has a high rate of fatality (62 5 per cent) while the average mortality for tularemia in the United States has been reported by the United States Public Health Service as 5 6 per cent (Foshay 6 0 Simpson 11 0 per cent) Death may occur within four days to nine months after onset

panied by general aching and weakness are followed by prostration, sweats and loss of weight Delirium and stupor may be present in the more severe cases The temperature records are not particularly characteristic, they may present a relapsing undulating, remittent or continuous type The constancy of the sequence of initial rise remission and secondary rise, however is striking in the cryptogenic type of the disease Continuous high temperature is noted in cases with extreme toxemia In cases of average duration the febrile period may last from ten to fifteen days and in the more severe forms the disease usually runs a course of from three to four weeks Febrile periods or elevation of temperature of one degree may persist for three weeks Eruptions of the skin in the form of a papular exanthema on the palmar surfaces or of roseola pustules and petechiae on any part of the body may appear at any stage in all forms of tularemia These rashes may be the result of toxic acion or bacterial emboli They heal by absorption or exfoliation

Enlargement of the spleen is evident in about one quarter of the cases and is not great, on rare occasions it extends from three to four finger breadths below the costal margin Tenderness and pain indicate the existence of a perisplenitis A slight to moderate polymorphonuclear leukocytosis (12 to 15 000 cells) may be noted during the course of the disease Secondary anemia is common The urine is diminished in amount and febrile in character Myalgia, arthralgia and neuralgia occur frequently

Cutaneous Tularemia—Within from thirty six to forty eight hours after the onset of the disease with slight painful enlargement of a lymph node the patient usually notices that a previous cut or sore is inflamed and tender This primary lesion evolves from a papular stage to a pustular stage with a necrotic plug The pustule is supplanted by a punched out ulcer with scanty serous discharge which ultimately is replaced by a scar Not infrequently painful lymphatics with or without subcutaneous nodules (nodular lymphangitis) resembling mycotic lesions extend from the ulcer to the regional epitrocheal or axillary lymph nodes The nodes vary in size from that of an almond to that of a small orange Sometimes several groups of nodes show reactions to a single primary lesion, for example, the axillary and supraclavicular nodes may react to a single ulcer on the shoulder Some lymph nodes suppurate in from one to twenty four months, others remain hard tender and palpable for periods up to twelve months and ultimately may require incision

Ophthalmic Tularemia—The primary localization is in the conjunctival sac it occurs unilaterally and rarely bilaterally Itching lacrimation photophobia and pain are early subjective symptoms which are accompanied by swelling of the pre auricular, parotid submaxillary and cervical lymph nodes The eyelids are swollen and the chemotic deep red conjunctivitis is studded with small discrete yellow nodules Occasionally both the palpebral and bulbar conjunctivae may be covered by a gray translucent organized exudate Punched-out ulcers follow the breakdown of the necrotic nodules A mucowatery or purulent discharge accompanies the conjunctivitis for from three to five weeks, after which the swelling recedes and complete recovery is the rule Suppuration of the regional lymph nodes is fairly common in ophthalmic tularemia Dacryocystitis, corneal ulcers permanent impairment of vision optic atrophy and blindness have been observed following perforation of the cornea

Cryptogenic Tularemia—The symptoms of a general systemic infection are characterized by fever profound toxemia with drowsiness or a typhoidal state abdominal distress and prostration It is of interest that with few exceptions (in Russia) the laboratory infections in persons who wore gloves when working on guinea pigs rabbits and mice revealed no primary skin lesion or tularemic lymphadenitis The cryptogenic type of tularemia however may be caused also by the bites of insects or by contact with rodents Severe pulmonary symptoms in at least 50 per cent of the cases or intestinal symptoms may follow

Pleuropulmonary Tularemia—The symptoms of pulmonary tularemia are variable and the diagnosis without laboratory aids is difficult The disease may begin as an inhalation infection with pulmonary symptoms

plished by supervision of interstate shipments of wild hares and of their sale for food in markets and restaurants

KARL F MEYER

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LEPROSY

Definition—Leprosy is a chronic infectious and contagious disease caused by the *Mycobacterium leprae* It presents a great variety of signs and symptoms owing to its tendency to implicate different tissues of the body, and frequently results in death either directly or indirectly as the result of grave complications

History.—There is evidence that leprosy occurred as long as two thousand years before the beginning of the Christian era Several references to the disease are made in the Old Testament It was common in Europe between the second and seventh centuries In the eleventh and twelfth centuries a great epidemic began which devastated the populations of England and the continent lasted for several centuries and gradually subsided during the sixteenth century In parts of the Orient (Egypt India China) it probably existed several thousand years ago In Europe the segregation of the victims of the disease in leprosaria led to a gradual local wiping out of the scourge so that at present the disease occurs only endemically and sporadically in different regions chiefly in Iceland Scandinavia Russia, northeastern Germany Galicia Hungary the Balkan Peninsula Spain Portugal southern France Greece Italy Turkey Africa and parts of South America

Incidence—Very few parts of the world are today entirely free from the disease Leprosy is common in China Japan the Philippines the East Indies Malaysia Australia India Turkestan Arabia and many other parts of Asia It is frequently encountered in Egypt northern and southern Africa, and many other coastal countries of that continent In the Western Hemisphere it is most common in the Hawaiian Islands Mexico and Central America the West Indies the northern countries of South America and in Paraguay In the United States foci have existed for many years in Louisiana Minnesota and South Carolina Sporadic cases are not infrequently seen in the larger cities of the Atlantic and Pacific seaboard because of immigration from countries mentioned above A few foci exist also in Canada

Etiology—Leprosy is caused by the *Mycobacterium leprae* which was discovered in 1873 by Hansen The mode of invasion of this organism is not definitely known but a considerable amount of evidence points to a probable transmission by inhalation In many lepers the nasal septum seems to be the first site of attack The mucosa of the gastro intestinal tract might be the path of contagion Some investigators believe that certain insects such as the bedbug mosquito fly itch mite etc play the role of intermediary host but this has not been confirmed That the disease is contagious there is no doubt but it is not readily contagious and can be transmitted from one person to another only after long continued and intimate contact Predisposing factors —bad hygiene filthy environment and unsanitary habits of living—are usually found to play a role in the transmission of the malady

Leprosy is most common in individuals between twenty and fifty years of age but it often attacks children It is rarely seen in infants The disease is much more often encountered in the male than in the female It is not hereditary and an inherited predisposition to it has never been demonstrated Much research work will be necessary to arrive at definite conclusions with respect

Diagnosis—Tularemia should be considered in every doubtful case of fever or atypical pneumonia in which the patient may have been exposed by contact with some animal The following immunologic and bacteriologic tests in the order mentioned are valuable diagnostic aids

(1) *Intracutaneous or percutaneous allergic skin tests* with detoxified formalin-killed *B tularense* as antigen (Foshay) may yield positive reactions on the third day of illness Since hypersensitiveness of the skin is a notable feature of tularemia in the early as well as the late stage of the disease this method deserves more frequent use than has been customary in the past The inflammatory response is similar to the reaction to tuberculin and attains maximal size forty eight hours after injection or application on the scarified skin

(2) *Agglutination and Complement Fixation Tests*—Specific antibodies in the blood never appear before the tenth or twelfth day of the disease and thus the agglutination test is of little help during the first period of the disease when it is most difficult to diagnose clinically The sera of patients with brucellosis furthermore may give positive reactions with tularemic antigens When repeatedly applied in order to determine a rise in the titer of the agglutinins the test is valuable and irreplaceable for retrospective diagnosis

(3) *Cultures* on dextrose cystine or thioglycolate blood agar, inoculation of guinea pigs with blood, pleural effusions and infected material or of mice with sputum during life and with blood from the heart at autopsy should be made when agglutinins are absent and the course of the disease suggests tularemia The danger to the laboratory worker who makes use of direct cultivation or animal tests should be recognized

Differential Diagnosis—Tularemia may masquerade in a variety of forms the signs and symptoms are so similar to many other acute infectious diseases notably influenza psittacosis atypical pneumonia undulant fever typhoid and septicemia that differential diagnosis is difficult The subcutaneous nodules and the enlarged lymph nodes have been diagnosed erroneously as sporotrichosis and at autopsy tularemia has been mistaken for tuberculosis In any locality where the infection is prevalent among rodents, the clinician must have tularemia in mind

Treatment—The treatment of tularemia is largely symptomatic During the febrile stage the patient should be at rest in bed Generous feeding is indicated Intravenous injections of physiologic solutions of sodium chloride seem to allay the severe toxemia According to a few reports sulfathiazole given in amounts of 2 Gm every three hours for the first two or three doses in order to insure an early high blood level and then 1 Gm every three hours has given encouraging results Sulfadiazine may also be tried Convalescent serum has not proved to be of value The specific antiserum prepared by Foshay was found ineffective when tested experimentally on animals (Francis and Felton) but in the hands of the discoverer when used early and in amounts of from 10 to 20 cc intravenously it apparently had a desensitizing effect and reduced the duration of the adenopathy and of the disease The use of vaccines during the acute stage has been tried and abandoned Local cutaneous lesions should not be incised, they are best treated by hot moist applications containing some germicide which makes the handling of dressings less dangerous Treatment by x ray has been tried with suggestively good results The most satisfactory treatment of the conjunctival inflammation is with hot applications and frequent lavage with warm physiologic salt solution Suppurating lymph nodes should be incised only after they show definite fluctuation Since febrile reactions and even chills may follow such a procedure surgical treatment of tularemia should be judicious

Prevention—Tularemia as an everlasting endemic and frequently epidemic disease of rodents and with a latent parasitism in insects cannot be eradicated Since no prophylactic vaccine has been worked out it is imperative that sportsmen butchers and those who live in regions where the infection prevails should be educated to the dangers of this disease Rubber gloves should be worn while dressing wild rabbits Laboratory workers should use face masks To render the meat of rabbits harmless thorough cooking is imperative Some reduction in the incidence of tularemia would be accom

they finally become elevated and nodular Usually they appear in crops In the larger lesions the circular central portion sometimes becomes white and depigmented As the malady progresses nodular infiltrations and thickenings of the skin appear on the forehead in the region of the eyebrows in the lobes of the ears and on the cheeks nose and mouth producing the so called leonine expression The outer portions of the eyebrows are lost The hair of the scalp remains unaffected These erythematous and nodular lesions may eventually attack any portion of the skin so that large surfaces become involved The fresh lesions are usually pink, red or violaceous in color the older lesions turn dark brown At times there is a distinct widening of the mouths of the hair follicles on the surface of the nodules The entire skin may present a peculiar dusky unhealthy hue the forearms and legs assume a dry scaly appearance like ichthyosis especially pronounced in patients with dark skins The nails frequently present small nodular infiltrations at their bases and are at times striated and distorted There is usually a well marked adenitis In some cases the legs swell as in elephantiasis While some of the nodules remain unaltered for long periods others soon ulcerate often as the result of injuries Spontaneous healing of ulcers and absorption of unbroken nodules may take place In advanced cases severe ulcerations go on to necrosis of the deeper tissues which results in loss of the fingers and toes (*lepra mutilans*) Many of the lesions leave depigmented or hyperpigmented scars

Small nodular lesions frequently develop on the mucous membrane of the pharynx nose larynx conjunctivae and less often on the tongue In some of these a softening and breaking down produces ulcerations contractures and scars The voice becomes hoarse The conjunctival lesions lead to keratitis scleritis and iritis and often to blindness Perforation of the nasal septum is not uncommon

The course of nodular leprosy is usually protracted it may last from ten to twenty years or even longer Most patients die of complications resulting from intercurrent affections such as tuberculosis pneumonia bronchitis nephritis etc in others death is caused by malnutrition, exhaustion and toxemia In rare instances the superficial evidences of the disease regress spontaneously and an apparent recovery takes place

Maculo-Anesthetic Leprosy (Lepra Nervorum) —Maculo anesthetic leprosy is characterized by macular lesions and large flat patches and by disease of the nerves Prodromal symptoms are often absent or pass unnoticed by the patient and are usually less evident than in the nodular type Usually beginning on the extensor surfaces of the extremities and on the back round, oval and gyrate macules and plaques appear distributed more or less symmetrically on both sides of the body Their edges are sometimes well defined at other times they merge imperceptibly with the normal skin The color of the lesions varies from red to violaceous or brown Rings and irregular polycyclic figures are formed the edges reddish brown the interiors yellowish or dull white in tint The surface is smooth and free of scales Sometimes acute erythematous patches appear which are ephemeral and simulate *erythema multiforme* In exceptional instances the earliest cutaneous lesion consists of a group of bullae which later become severe ulcers

The affected areas of skin are at first hyperesthetic and pruritic but as the malady progresses they become anesthetic because of implication of the nerve trunks The superficial nerve trunks such as the ulnar tibial peroneal and postcervical become thickened and present fusiform swellings which may often be readily palpated This invasion of the nerve trunks and their branches results in loss of sensibility to touch heat and cold As time goes on complete anesthesia supervenes Traumatisms and burns occur without the patient s knowledge, these ulcerate and suppurate and often result in frightful deformities Trophic changes occur in various groups of muscles the interossei thenar and hypothenar eminences frequently being first affected Contractures of the tendons then ensue and produce the characteristic clawhand or leper claw Atrophy of the facial muscles gives the features a masklike appearance Perforating ulcers of the soles of the feet are common In advanced cases there may be extensive mutilations

to modes of transmission, sites of inoculation, the role of insects as intermediary hosts of the bacterium the susceptibility of exposed persons, and many other phases of the etiology of the disease

Morbid Anatomy —Leprosy is a neoplastic disease included in the group known as infectious granulomas The new growth produced by the causative organism the *Mycobacterium leprae*, is a granuloma composed of connective tissue cells epithelioid cells vacuolated giant cells together with mast cells lymphocytes and plasma cells Scattered through this infiltrate are variable numbers of large ovoid cells the so called *lepra cells* the exact nature of which has not been definitely determined

The bacterium of leprosy closely resembles that of tuberculosis both in respect to its morphology and its reactions to stains It is from 5 to 6 microns in length and frequently presents a beaded appearance sections of tissue often reveal enormous masses and clumps of bacteria, the organisms also occur in the lepra cells in the walls of blood vessels and in the sheaths of nerves In the cutaneous nodules of leprosy in discharges from ulcers and from the mucosa of the nose and pharynx large numbers of organisms are frequently found When the disease is advanced bacteria may be found in all the viscera particularly in the liver and spleen Cultures of the organism on artificial media have been grown successfully by Duval Clegg, Currie Wellman Hollmann and others Duval among others recently succeeded in inoculating animals with the disease Honeij found the organism in the blood of nine out of twenty eight lepers More recent investigations seem to throw considerable doubt on the results of the work thus far carried out on cultural and animal inoculation experiments (See Lepra Handbuch der Haut- u Geschlechtskrankheiten Vol X/2 Edited by J Jadassohn Julius Springer Berlin 1932)

The histopathologic picture of sections from leprous tissue often closely simulates that of syphilis and of tuberculosis when bacteriologic identification of the causative organism fails differentiation of these diseases by means of microscopic examination of tissue is often a difficult task

Symptoms —Leprosy is characterized by a great variety of symptoms partly because of the fact that different tissues of the body are concurrently affected and partly because of the appearance of secondary lesions as complications

The *period of incubation* is extremely variable it may be several months or perhaps twenty or thirty years In one of the writer's patients it was estimated to be twenty three years

The *preeruptive manifestations* are those common to other infectious diseases and consist of backache, pains in the muscles and joints digestive disturbances, neuralgias and headaches *Rhinitis* is a common prodromal symptom Sometimes there are attacks of fever simulating malaria Occasionally prodromal symptoms are lacking or the nervous system is chiefly implicated and there may be attacks of pruritus hyperesthesia, anesthesia and various disturbances of sensation particularly with respect to response to heat and cold

According to the main point of attack of the invading organisms—the skin or the nervous system—the disease assumes two clinical forms—nodular leprosy and maculo-anesthetic leprosy A third form mixed leprosy presents the symptoms of both varieties one merging with the other Clinical symptoms are classified as (1) lepromatous (2) neural and (3) mixed The new classification recently adopted uses the symbols C (cutaneous) and N (neural) Later the symbol L (lepromatous) was substituted for C (cutaneous) Mild moderate and advanced cases are labelled respectively 1 2 3 Thus a mixed case with severe cutaneous lesions and mild neural changes would be designated as L3 N1 In the United States most of the patients have the mixed form of disease

Nodular Leprosy (Lepra Tuberosa) —Nodular leprosy is characterized by the formation of nodules or lumps in the skin The lesions are usually preceded by reddish and brownish red spots which vary in size from ¼ inch to several inches they may be flat or slightly elevated the surface is smooth and frequently has a peculiar velvety texture These develop most commonly on the back of the hands and feet and on the face Some spots gradually fade without leaving a trace other slowly increase in size until

giene etc The prognosis of the nodular and mixed varieties is far less favorable

Treatment—Like tuberculous patients lepers are apt to contaminate their immediate surroundings with secretions and excretions Coughing sneezing and spitting presumably play an important part in the dissemination of the disease, the urine and feces also harbor bacteria Patients with open lesions—excoriations ulcers secreting wounds etc both of the skin and mucosae—should be strictly segregated The United States Government maintains a leprosarium in Louisiana Large cities provide housing and facilities for the segregation of lepers Patients with the maculo anesthetic variety especially when they have no demonstrable excoriated lesions in the nasal buccal or pharyngeal mucosae need not generally be strictly segregated but they should be required to take all precautions against contamination of others Long continued association with the nonleprous must be avoided rooms bedding wearing apparel cooking utensils etc must be used only by the patient all precautions being carried out just as in pulmonary tuberculosis

Many remedies have been used nearly all of them unsuccessfully with one exception namely *chaulmoogra oil* and its derivatives

Pure chaulmoogra oil may be administered *per os* in doses of from 5 to 60 drops three *times daily it may* be taken with a lump of sugar or mixed with milk or Vichy water Some patients bear it well in others it causes gastritis which necessitates cessation of the medication Many patients have however improved strikingly after long continued ingestion of this oil

The modern treatment and the most efficacious consists in subcutaneous and intramuscular injections *Mercado s formula* which was extensively employed by Heiser with very good results is as follows

Chaulmoogra oil	60 cc
Camphorated oil	60 cc
Resorcin	4 Gm

From 5 to 60 drops or even more of this mixture are injected into the gluteal muscles two or three times per week This often gives rise to considerable pain at the site of injection Currie and Hollmann claim to have had better results with

Iodine	1 Gm.
Oil of eucalyptus	8 cc
Camphor	2 Gm
Olive oil	147 cc
Chaulmoogra oil	150 cc

mixed in the order given using heat The maximum dose is 10 cc, given intramuscularly once a week

Apparently the most promising results thus far obtained have been from the use of the *fatty acids of chaulmoogra oil* Hollmann and Dean, in the course of their investigations in the Hawaiian Islands have for some years been administering the ethyl ester of the fatty acids of the oil with very promising results A large proportion of their patients have been helped, and a considerable number apparently cured—that is cured in the sense that lesions become undemonstrable and bacteria findings negative This product is on the market and may be obtained in large cities It is injected into the gluteal muscles twice a week in doses ranging from 10 drops to 1 drachm Treatment must be continued over prolonged periods—two three even five years—with intervening periods of rest

Fortnightly determinations of the sedimentation rate should accompany chaulmoogra therapy and when the rate is high treatment should be temporarily omitted

Treatment by means of fever therapy is now in the experimental stage

Collier and McKean have reported experiments with diphtheria antitoxin and diphtheria toxoid in patients with repeated lepra reactions As controls a number of similar patients were given injections of tetanus antitoxin and several others received antivenom The following beneficial results have been noted in approximately 120 patients treated by this method immediate reduction of leper nodules plaques and tuberculoids rapid improvement in leper reactions usually with lasting effects return of sensations to some previously anesthetic areas reduction of enlarged nerves particularly the ulnar nerves general physical improvement and fragmentation and granulation of the bacilli

Unfortunately the favorable results reported by Collier and McKean have not been confirmed by other investigators who have employed Collier s therapy on large

This variety of leprosy is more insidious and more protracted than nodular leprosy Death often results from complications in volving the liver and kidneys or from malnutrition and exhaustion

Recently the application of the allergic concept in infectious diseases has contributed to our knowledge of the causes of "tuberculoid' forms of leprosy with their relative *paucity of bacteria These were first* observed and interpreted by J Jadassohn (1898)

Mixed Type —Combinations of the symptoms of nodular and maculo anesthetic leprosy *are frequently encountered* and constitute the syndrome of the so called mixed type' The predominating lesions are usually of the nodular type in the earlier stages but later assume the symptoms characteristic of nerve involvement

Diagnosis —An advanced case of leprosy cannot be mistaken for other diseases but in the prodromal stage diagnosis is attended by great difficulties The patient especially if he comes from a region where the disease is endemic, should be stripped and examined in a good light Mottling and yellowish brown discolorations of the skin associated *with areas of hyperesthesia* anesthesia and paresthesia should excite suspicion The following changes should be carefully looked for thickening of superficial nerve trunks, thickening of the ear lobes and supra orbital regions loss of eye brows, nodules and deformities of the nails atrophy of the muscles and nasal pharyngeal and laryngeal lesions The earlier erythematous patches sometimes resemble *erythema multiforme* but are of longer duration there is no sensation of burning or smarting on the contrary the lesions are often anesthetic Nodular leprosy sometimes simulates *syphilis* but the duration of the syphilitic eruption is much shorter The history of a primary lesion and secondary eruptions together with evanescent lesions of the buccal mucosae should be taken into consideration hyperesthesia anesthesia and paresthesia are lacking The *Wassermann reaction* is frequently positive in nonsyphilitic lepers affected with nodular leprosy A recently published modification of the test perfected by Kolmer seems destined to become of practical use in the laboratory *differentiation* of the two diseases The *bacteriologic diagnosis* is of course the scientific method of differentiation, in leprosy, smear preparations should be made from the nasal and buccal secretions, *from the surface of ulcers* and excoriations and even from the serum of a curetted papule, in an attempt to find the specific bacteria In patients with suspected syphilis search should be made for *the Spirochaeta pallida* in the secretions of moist lesions, the serum of curetted papules or in the fluid of aspirated lymph nodes The result of the Wassermann test is significant In both diseases microscopic examination *of sections of the tissue is often* decisive The therapeutic test in syphilis is of great value

Certain manifestations of *lupus vulgaris* of *mycosis fungoides* of the *hemorrhagic sarcoma* of Kaposi of *vitiligo* of the comparatively rare *annular syphilids* and of a few other eruptions characterized by rings gyrate and polycyclic figures are sometimes apt to cause confusion in differential diagnosis but in the great majority of instances in which these diagnoses might obtrude themselves the actual difficulties encountered are more imaginary than real

In syringomyelia which is apt to be confounded with leprosy, there is an alteration of the pain and temperature sense without loss of tactile sensibility—the so called dissociated anesthesia , the occurrence of pain *less whitlow* and various *trophic distur*bances in the absence of cutaneous manifestations is evidence of this disease and not of leprosy

Prognosis —Until the last few years the outlook for the leper has always and everywhere been regarded as hopeless Despite the fact that some patients with spontaneous regression of symptoms and temporary freedom from lesions have been encountered the overwhelming proportion die wretchedly Recent investigations of the chemotherapeutic properties of the ethyl esters of chaulmoogra oil have however changed the prognosis from 'very bad to hopeful Reports of cures are now appearing in the *literature*

Patients suffering from the less virulent maculo anesthetic variety are apt to live for one or more decades in comparative comfort *depending upon environment nursing by*

countries bovine herds remain heavily infected and the incidence is estimated as high as 40 per cent in Great Britain

Incidence in Man —No branch of the human race has escaped the touch of tuberculosis and this is true in whatever part of the world man abides The severity of its effects however varies greatly in different communities Although the infection is very common most people survive The occurrence of infection mortality and morbidity therefore must be analyzed separately Formerly in most communities almost all adults reacted to the tuberculin test and this is still true in some sections In the United States however there has been a decided decline in the rate of infection and it is estimated now that 50 per cent or less of the population would react In Detroit for instance Douglas and Harmon in 1938 reported the following results of the tuberculin skin test among the population of that city

Age	*Number tested*	*Percentage positive*
0– 9	20 585	5.9
10–19	22 441	18.9
20–29	21,304	38 0
30 and over	34 862	44.3
Not stated	222	50.2
Total	99 414	29.2

In congested urban centers infection is more prevalent as indicated by the observations of Lincoln Raia and Gilbert in the wards and clinic of Bellevue Hospital between 1930 and 1936 Among 11 136 children tested reactions were elicited in 0 7 per cent of those tested between birth and six months of age 5.3 per cent between six and twelve months 10 per cent between one and two years 15 1 per cent between two and four years 18 1 per cent between four and six years 23.5 per cent between six and eight years 26.9 per cent between eight and ten years 32 6 per cent between ten and twelve years Among 149 744 college students in the United States according to the 1941 report of the American Student Health Association the incidence of tuberculin reactors was 20 7 in 100

Some of these figures are misleading because of the inadequacy of the dose of tuberculin Carnes studies of autopsies performed in Baltimore during 1938–1940 indicated according to him that 90 per cent of the adult population of that city has been infected Some he thinks are so lightly infected that they may lose their tissue hypersensitivity and fail to react to the tuberculin test In a similar study in the Washington County Hospital Hagerstown Maryland during 1938–1940 Lande and Wolff found tuberculous lesions in 48 4 per cent of 128 subjects

Mortality from the disease also varies greatly in different parts of the world Before the outbreak of World War II it was less than 50 per 100 000 population per year in Denmark Netherlands Australia New Zealand and the United States In England and Wales Italy Germany and Sweden the rate was between 50 and 100 per 100 000 In Japan and Finland it approximated 200 and in Chile Puerto Rico and the Philippines it exceeded 250 A rather steady and striking decline in mortality had been observed for many years in various countries In the United States the rate per 100 000 per year declined from 202 in 1900 to 160 in 1910 114 in 1920 71 in 1930 and 44 4 in 1941 However the present war has brought a reversal of this trend in England Germany and France and probably in many other countries In England where the death rate has risen 13 per cent the increase of tuberculous meningitis among children has been especially high In this country tuberculosis now stands seventh among the leading causes of death but it is still the leading cause between the ages of fifteen and forty five Death is due to the pulmonary form of the disease in about 91 per cent of all cases and to nonpulmonary or generalized forms in 9 per cent

Morbidity is variously estimated In most communities approximately 2 new cases of the disease are reported each year for every death It is generally estimated that there are approximately 5 active clinical cases for each annual death In the United States therefore with its 59 251 deaths in 1941 the estimate would be approximately 296 000 active cases Case-finding surveys among apparently healthy people disclose about 2 per cent of the adults harboring lesions recognizable in the roentgenogram Approximately one half of these are usually found to be active or potentially active

groups of lepers In the overwhelming majority of cases no beneficial effect was demonstrable In patients who appeared to be benefited improvement was negligible and ephemeral

Cutaneous lesions—plaques nodular infiltrations and ulcerations—often respond favorably to exposure to the roentgen ray Infiltrated lesions and deep seated ulcers should be treated with filtered rays, the average dose is 300 r filtered through 3 mm of aluminum screen once every three or four weeks Radium should be employed for lesions in the mouth and about the eye Antiseptic and general surgical procedures are necessary in advanced cases Frequent hot baths with sodium bicarbonate dissolved in the water are beneficial Change of climate and the use of a good tonic such as a combination of iron quinine and strychnine are at times helpful



Fig 26—A well developed case of nodular leprosy in a native of Odessa, Russia The patient was sixty five years old had been in America for twenty five years and had noted her first lesion about five years ago (J A Fordyce)

FRED WISE

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TUBERCULOSIS

Definition—Tuberculosis is an infectious disease caused by the tubercle bacillus Tuberculosis is a widespread disease of man and animals uniformly fatal in some seldom if ever in others acute and generalized in some individuals chronic and localized in others pathologically the disease is characterized by the development of tubercles and diffuse inflammatory lesions

History—Archeologic discovery of skeletons bearing the marks of tuberculous lesions indicate that the disease existed in remote antiquity Described in the earliest medical records it was called consumption or phthisis because of its most conspicuous external feature wasting Long considered to be of many varieties and origins the unity of the disease was first recognized by Laennec The correctness of his conceptions was disputed by many including Virchow and was not universally acknowledged until Koch in 1882 isolated the specific organism and reproduced the disease experimentally The avian type of bacillus was isolated in 1890 by Maguccı and the bovine type in 1898 by Theobald Smith

Distribution—Under certain conditions fish amphibians fowls and animals may develop tuberculosis although in their wild state these classes are not very susceptible Animals in captivity sometimes fall easy prey to the disease Among domesticated animals it is seldom observed except in cattle swine and gallinaceous birds In the United States an active plan of eradication of tuberculosis from cattle has been highly successful so that the incidence is now well under 1 per cent even less among swine In many

rate in old men as compared with old women may involve similar forces

Allergy and Immunity.—These factors which begin to assert themselves shortly after the development of the first lesion modify subsequent reactions Koch demonstrated that an animal previously inoculated with tubercle bacilli slowly develops an indolent and usually nonulcerating lesion at the site of inoculation and dies with progressive and generalized tuberculosis after the lapse of a few months Within a few weeks after the inoculation the tissues for the first time become sensitive to tuberculin This altered reaction is known as tissue hypersensitivity a form of allergy Similarly Koch found that a second inoculation of bacilli into the skin of a previously infected animal produces a lesion which behaves differently from the primary The local reaction is rapid and intense with a tendency to abscess formation ulceration extrusion of the necrotic matter and subsequent healing Dissemination of bacilli from this focus through the lymph and blood streams is much slower and less severe This the Koch phenomenon is a manifestation of allergy (tissue hypersensitivity) and of acquired relative immunity the mechanics of which has been identified only partly Weakly concentrated humoral antibodies may be demonstrated Phagocytosis and the deposition of fibrin barriers at the site of the lesion are accelerated and intensified If the primary infection was not overwhelming or was accomplished with an attenuated strain of bacilli the animal now may survive the effects of reinfection for many months In the human being tissue hypersensitivity which usually develops within three to six weeks after the first infection helps to explain certain intense inflammatory reaction such as serous pleurisy Acquired immunity which is never absolute seems to develop much more slowly and to be maintained despite the subsidence of tissue hypersensitivity ('nathergic immunity Birkhaug) The latter judged by the tuberculin test sometimes fades and disappears as lesions heal but it is not proved that acquired immunity is lost entirely

Heredity.—The superior resistance of certain races such as the Jews suggests that hundred of years of experience with tuberculosis results in the elimination of the susceptible and the survival of relatively resistant members It has been intimated that specific immunity may be inherited to a degree but this has never been proved The evidence is more suggestive that some racial stocks have a stronger or weaker natural resistance—a genetic character

Constitution and Race.—Clinicians have often described types of people thought to be susceptible to tuberculosis *e g* the asthenic thin skinned silken haired Titian blond Recent statistical studies such as that of Wolff and Ciocco focus attention on the importance of constitution with regard to susceptibility and resistance Kallmann and Reisner studying monozygotic and dizygotic pairs of twins found that the chance of developing tuberculosis increases in direct proportion to the degree of blood relationship to a tuberculous case Lurie has been able to breed families of rabbits in which the greatly varying resistance is a function of their genetic constitution The higher mortality among Negroes in many parts of the world is ascribed by some entirely to poor living conditions However the striking tendency of the lesions to undergo caseation rapidly and the greater liability to lymphohematogenous dissemination of the infection indicates that there is a real constitutional peculiarity in this race In the United States the tuberculosis death rate for Negroes is three to five times that among whites in 1910 11 per cent of all deaths from tuberculosis occurred in colored people while in 1940 the proportion was 26.3 per cent indicating a less rapid decline of mortality among Negroes as compared with whites

Age and sex influence the behavior of the disease whether this originates in a recent primary infection or in a recent extension from remotely established lesions Generalized tuberculosis is much more common in early childhood Chronic pulmonary tuberculosis characteristically begins to appear in the second and third decades Those who have lived to the fourth decade without the appearance of a pulmonary lesion seldom develop the disease Figures 27 and 28 portray the mortality experience with relation to sex and age

Epidemiology —Since man may be infected by the human or bovine type of the bacillus the source is usually traced to another person with tuberculosis or to a tuberculous cow Contaminated milk is seldom implicated in this country but in others it is considered responsible for much human disease especially abdominal tuberculosis In Scotland it has been estimated that as many as 8 per cent of the cases of pulmonary tuberculosis are due to the bovine type of bacillus and the incidence is higher in other lesions such as tuberculous lymphadenitis osseous tuberculosis and tuberculous meningitis The more common source of infection is the human case of tuberculosis with pulmonary cavities draining through the bronchi and giving rise to sputum laden with organisms Other lesions such as superficial tuberculous sinuses may constitute sources and the possibility of transmission through contaminated urine or feces occasionally has to be considered The means of transmission however is usually contaminated air inhaled by persons in the vicinity of the sufferer Direct mouth to mouth transmission may occur particularly in the case of nurslings As would be expected therefore many new cases of tuberculosis are discovered near the abodes of people previously afflicted In this sense the disease is frequently familial or household and it is also somewhat more prevalent among the personnel of hospitals or other institutions caring for tuberculous patients Infection has been shown to be almost inevitable among young children who have such opportunities in the home for close contact with the 'open case' usually in an adult Intimacy and frequency of contact favor heavy and repeated infection thus more serious disease

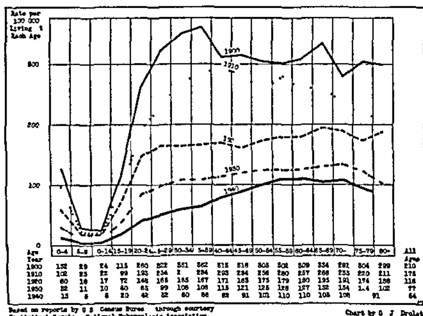
Bacteriology —The tubercle bacillus (*Mycobacterium tuberculosis*) exists in three types the human (*typus humanus*) the bovine (*typus bovinus*) and the avian (*typus gallinaceus*) Man may be infected by the human or bovine types seldom by the avian type Animals are infected most often by the bovine type This varying pathogenicity may be used to help identify the type Thus cavia are susceptible to infection by the bovine and human types but not the avian rabbits are susceptible to the bovine and avian, much less to human fowls usually are susceptible only to the avian The bacillus is a rod shaped organism distinguished particularly by its acid fastness to stains Granular forms have been recognized but the existence of a virus stage is not generally acknowledged The bacillus grows slowly and aerobically on various culture media R J Anderson particularly has studied the chemistry of the bacillus which is made up mainly of lipids waxes polysaccharides and proteins There is no capsule While the organism is tenacious of life and may survive many months in the dark or when refrigerated, it survives only a short time in rooms well supplied with unfiltered daylight (C R Smith) and it is killed by boiling in water for two minutes or pasteurization at 60° C

Organisms isolated from human cases are with rare exceptions virulent in guinea pigs The pathogenicity may be attenuated by prolonged growth on certain artificial media such as the bile treated potato medium of Calmette and Guerin and Smithburn has succeeded in altering this property merely by varying the hydrogen ion concentration of the medium

Etiology —*Man is relatively resistant* to invasion by tubercle bacilli Infection is common but less than 10 per cent of all those infected die of the disease This bespeaks a native resistance which as a rule *is highly effective* Its precise nature is not understood and it is difficult to distinguish it from the numerous other factors which influence the course of the infection Natural resistance varies with age Young infants may go on to develop generalized tuberculosis soon after the first infection and the case fatality rate at this time of life, calculated on the basis of the number infected is higher than at any other age despite the fact that only about 1 per cent of all deaths in the United States before the age of five are due to tuberculosis The mortality rate is generally low between the ages of five and adolescence when there is an abrupt rise reaching its peak in females in the early twenties somewhat later in males This suggests strongly that biologic influences associated with puberty alter natural resistance The relatively high death

tendency before the discovery of insulin Pulmonary tuberculosis is a frequent com plication of congenital pulmonic stenosis but when present usually runs a relatively mild course in association with mitral sten osis Tuberculous patients frequently with stand pneumococcal pneumonia well unless the functional reserve has been almost de- pleted previously Suppurative pneumonia or abscess however, may lead to breaking down an arrested tuberculous focus and sub sequent extension of the infection from it

Morbid Anatomy—The inflammatory reaction to infection by the tubercle bacillus times termed a productive tubercle because of its tendency to proliferate add to its mass and displace surrounding tissues Either may be progressive or retrogressive Progression is evidenced by changes in the extent and character of the lesion The cen tral elements where as a rule bacilli are most heavily concentrated become coagu lated undergo caseous degeneration and finally liquefaction Not only the lesion itself but also the invaded tissues are involved in the destruction Because of its increasing tension the abscess may dissect a path through surrounding structures but is prone



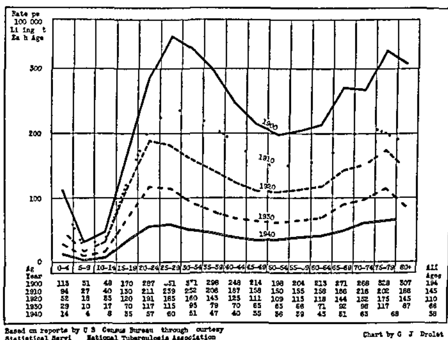
Age / Year	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-	75-79	80+	All Ages
1900	132	29	24	115	260	322	351	362	315	316	305	302	309	334	281	304	299	210
1910	102	23	22	99	193	234	[illegible]	284	293	284	256	280	257	266	235	220	211	178
1920	60	18	17	72	148	168	165	167	171	163	175	179	180	195	191	174	156	118
1930	32	11	10	40	65	99	106	106	115	121	125	128	127	152	154	1.4	102	77
1940	15	5	5	20	42	52	60	88	82	91	101	110	110	105	106	91		64

Fig 28—Male tuberculosis death rate by age years 1900 1910 1920 1930 1940 United States (expand ing) death registration area

varies morphologically from the tubercle to a diffuse exudation of cellular and humoral elements The isolated tubercle made up of giant cells lymphocytes and so called epi thelioid cells represents a relatively mild reaction resembling that to a foreign body Diffuse inflammation consists chiefly of plasma fibrin leukocytes large phagocytic cells and sometimes erythrocytes Such dif ferent types of lesions may develop simul taneously in the same or different tissues or may exist side by side Generally speaking the exudative lesion so called because it is an exudation of inflammatory products into tissue spaces is more acute sometimes in tensely so The epithelioid tubercle is some to find an outlet through ulceration Through this vent then the liquefied mat ter is discharged and characteristically there is left behind a fistula which may be perma nent or occasionally may heal as granula tions proliferate from the base of the ulcer

Healing of tuberculous lesions occurs mainly by resolution absorption and fibrosis Resolution operates chiefly in exu dative lesions and is indicated by the gradual disappearance of serous and cellular elements first at the periphery proceeding centrally A central caseous focus if it is not sloughed out by ulceration may become in spissated slowly and later infiltrated by mineral salts chiefly calcium in time the

Physiologic and Psychologic Influences — Pregnancy is recognized in some women to activate pulmonary tuberculosis Impaired nutrition particularly when there has been a deprivation of essential vitamin and mineral elements may lower resistance The current increase in tuberculosis deaths in the war torn countries appears to be due in part to the limitation of food supplies there was a similar rise in first World War Psychologic influences usually are not conspicuous although one gets the clinical impression that the unstable emotional person is less resistant There is some evidence is greatest *Occupation* which is a good index of social economic status illustrates this strikingly The death rate is highest among unskilled laborers and lowest among those in professions including physicians A specifically dangerous occupation with relation to tuberculosis is that which involves exposure to silicious dust This hazard exists in many industries and the death rate from tuberculosis among the employees sometimes is six to eight times that among other comparable groups Meteorologic conditions have an influence especially upon labile tuberculous lesions and help to explain the



Ag Year	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+	All Ages
1900	113	51	48	170	287	[illegible]51	3[illegible]1	296	248	214	198	204	213	271	268	328	307	194
1910	94	27	40	130	211	239	252	206	187	158	150	155	158	186	216	202	188	145
1920	52	18	33	120	191	165	160	143	125	111	109	115	118	144	152	175	145	110
1930	29	10	17	70	117	115	95	79	70	65	65	66	71	92	98	117	87	66
1940	14	4	8	35	57	60	51	47	40	35	36	39	45	51	63	68		58

Fig 27 —Female tuberculosis death rate by age years 1900 1910 1920 1930 1940 United States (expanding) death registration area

that tuberculosis is more likely to develop in schizophrenics The death rate is usually high in institutions for the mentally ill but this seems now to be ascribable to intimate exposure and to be largely correctible by isolating the infectious cases

Environment —Geographic location alone does not seem to be a major influence Tuberculosis is a serious problem both in the Alaskan Indians and in Puerto Ricans Social economic and occupational factors are much more important Ignorance poor housing and overcrowding all are recognized as powerful evils Haven Emerson points out that in cities tuberculosis is prevalent in those sections where nonpayment of taxes trend to activation in the late winter and spring

Trauma —Previously healthy traumatized tissue is not liable to be invaded by tuberculosis except by direct extension from an immediately adjacent lesion Direct traumatization of tuberculous tissue however may be aggravating In the case of pulmonary tuberculosis occasionally a severe trauma of the chest may result in such manifestations as hemoptysis bronchogenic dissemination of the infection or pleural rupture with secondary empyema

Intercurrent Disease —Diabetes if uncontrolled especially in young people predisposes to serious tuberculosis a conspicuous

a walnut but usually the size of a pea It is situated most often near the pleura in a lower lobe or the lower part of an upper lobe usually the right From pathologic evidence and a great deal of experimental work it has been shown that tubercle bacilli soon escape from this initial focus and traverse the lymphatics to the bronchopulmonary and tracheobronchial nodes where secondary lesions develop This combination of pulmonary focus and tributary lymphadenitis (occasionally with intervening tubercles) is called the primary complex Commonly the lesions become arrested at this point and undergo regressive changes leaving only small fibrous or calcified residues which may remain permanently

Occasionally the disease is progressive from the very start particularly in infants and young children While the focus in the pulmonary parenchyma may progress it is much more common to find the continuing changes in the lymph nodes of the mediastinum These may enlarge so as to fill the mediastinum and compress contiguous structures and occasionally a caseous node may ulcerate into the trachea or a large bronchus there to discharge its contents However a more common sequence is contamination of the blood stream by direct ulceration of a vessel or much more often through the escape of bacilli by way of the lymphatics into the innominate vein Such mechanisms account for the high proportion of deaths from generalized tuberculosis among infants If the primary infection is postponed until later in life this tendency appears to be less striking *e g* in young adults the occurrence of large lymphatic lesions and of blood stream dissemination is much less frequent than it is in infants Exceptions to this rule are observed especially in young adult Negroes

Lymphohematogenous Dissemination — In young children there is pathologic evidence to suggest that infection of the blood stream may occur at almost any period of development of the primary lesions until they become encapsulated (postprimary dissemination) and occasionally during their reactivation after many months or years of latency

The behavior of lymphohematogenous disseminations depends first on the point of emergence of the invading organisms into the blood stream A tubercle sloughing into a pulmonary vein liberates bacilli which quickly gain access to the systemic arteries and immediately are distributed widely through the body in the returning venous stream those which have not been arrested elsewhere may lodge in the lungs More often however especially in infants the point of emergence is a caseous mediastinal lymph node whence the bacilli shortly enter the venous blood Thus the lungs again suffer the heaviest onslaught and if most of the bacilli should be screened out here only a minority may find their way into the arterial stream for general distribution These differences help explain variations in the picture of hematogenous tuberculosis such as the finding of lesions in the lungs when there are only few or none to be discovered in other parts

Bacilli entering the blood stream are rather promptly removed and apparently arrested in the tissues if one interprets correctly the usual failure to recover the organisms by blood culture However the frequency of blood stream invasion even among those who never develop tuberculosis in a clinical form is attested by the common finding at autopsy of old encapsulated foci in the liver kidneys spleen lymph nodes and other tissues

The great variation in the number and severity of hematogenous lesions is related somewhat to the mass of the infecting dose, its physical suspension and the rate or repetition of its discharge Abrupt liberation from a liquefied caseous focus of myriads of tubercle bacilli which become finely dispersed in the blood may be the initiation of acute generalized miliary tuberculosis in contrast the escape of a single clump may result in only a single lesion at some distant point as in the kidney Numerous bacilli collected into a relatively few clumps and so deposited at various sites may produce the picture of subacute generalized tuberculosis in which many of the lesions are larger than miliary and become grossly caseous When bacilli are liberated in small doses at varying intervals of time the result is the establishment of hematogenous foci of varying age and chronicity as indicated by the

caseous mass especially if it is only several mm in diameter may be entirely transformed through a chalky stage into a hard calcareous deposit If this becomes sterile it may undergo true ossification More often the transformation is incomplete and a partially calcified cheesy collection remains in which tubercle bacilli may remain viable many years *As implied caseous collections* of material size seldom become absorbed completely but constitute infectious foci *from which disseminations may occur* after a longer or shorter period of latency Such latency depends largely on the character and intactness of the enveloping fibrous capsule which gradually forms This at first is tuberculous granulation tissue but eventually may be transformed into thick connective tissue Resolution does not necessarily antedate fibrosis The gray tubercle for instance may be transformed slowly into a fibrous mass perhaps with only a minimal caseous center Eventually all tuberculous elements may disappear leaving only a scar without marks to identify its specific origin In other circumstances stimulated presumably by the slight but persistent diffusion of toxins from the necrotic center of a lesion fibrosis may extend centrifugally into relatively healthy tissue, the organization of exudate within undestroyed alveoli has been designated carnification Fibrosis often increases in density and thickness until it acquires an almost cartilaginous *consistency Its shrinkage produces* mechanical effects which vary with the structure involved There are retractions constrictions and distortions and sometimes these lead to profound functional disability

Once a liquefied tuberculous lesion has sloughed and communicates with a cutaneous or mucous surface secondary infection with pyogenic bacteria may occur contributing toward chronicity

Modifying Influences—The properties of tuberculous lesions while essentially identical are influenced by a great many factors One example is the nature of the tissue attacked The skin is relatively very resistant and seldom infected from without Compact organs like the liver or spleen are seldom involved in destructive tuberculosis but the contrary is true of the lungs It is easier to infect the lungs than the mucosa of the nose mouth or intestine, this difference appears related in part to mechanics such as ciliary action and the *movements* of mucus or ingested food which prevent long contact of the bacillus with the mucosal *surface This has been cited to help* explain the predilection of the ileocecal region for tuberculous invasion since intestinal *motility is slower here than above* The behavior of a lesion often is conditioned by opportunities of localization thus diffuse *inflammation* of the pleura with serous exudation occurs much more often when the visceral and parietal layers are separated as by artificial pneumothorax An obvious explanation is that this separation prevents the fibrinous agglutination of the inflamed surfaces which usually serves to confine the process Other relationships are recognized such as the proximity of involved parts thus a common complication of tuberculous salpingitis is pelvic peritonitis Similarly vascular relationships often determine not only the paths of transport of the infection but also the sites of implantation

Pathogenesis—Almost any tissue may be successfully inoculated with tubercle bacilli and the primary lesion has been observed in a number of sites including the eye the finger the prepuce (following circumcision rites) the tonsil the intestine and the lung A relatively high proportion of abdominal tuberculosis occurs in countries where there are great chances of infection by the *ingestion of contaminated* raw milk However the pathologic investigations *of* Ghon and others following him have shown that the common portal of entry is the lung and the common means of infection inhalation Presumably a few tubercle bacilli may be carried into the mouth alimentary canal nose trachea or bronchi without causing lesions indicating prompt and complete effectiveness of the physiologic defenses It may be reasonable even to assume that lethal phagocytosis may occur sometimes when the organism has reached an alveolus Under suitable conditions however inhaled bacilli reaching the pulmonary alveoli result in a lesion which when identified usually is of an exudative nature a small *focus* of bronchopneumonia As Ghon first described this primary focus is usually single varying in size from that of a hemp seed to that of

a walnut but usually the size of a pea It is situated most often near the pleura in a lower lobe or the lower part of an upper lobe usually the right From pathologic evidence and a great deal of experimental work it has been shown that tubercle bacilli soon escape from this initial focus and traverse the lymphatics to the bronchopulmonary and tracheobronchial nodes where secondary lesions develop This combination of pulmonary focus and tributary lymphadenitis (occasionally with intervening tubercles) is called the 'primary complex Commonly the lesions become arrested at this point and undergo regressive changes leaving only small fibrous or calcified residues which may remain permanently

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Lymphohematogenous Dissemination — In young children there is pathologic evidence to suggest that infection of the blood stream may occur at almost any period of development of the primary lesions until they become encapsulated (postprimary dissemination) and occasionally during their reactivation after many months or years of latency

The behavior of lymphohematogenous disseminations depends first on the point of emergence of the invading organisms into the blood stream A tubercle sloughing into a pulmonary vein liberates bacilli which quickly gain access to the systemic arteries and immediately are distributed widely through the body, in the returning venous stream those which have not been arrested elsewhere may lodge in the lungs More often however, especially in infants the point of emergence is a caseous mediastinal lymph node whence the bacilli shortly enter the venous blood Thus the lungs again suffer the heaviest onslaught and if most of the bacilli should be screened out here only a minority may find their way into the arterial stream for general distribution These differences help explain variations in the picture of hematogenous tuberculosis such as the finding of lesions in the lungs when there are only few or none to be discovered in other parts

Bacilli entering the blood stream are rather promptly removed and apparently arrested in the tissues if one interprets correctly the usual failure to recover the organisms by blood culture However the frequency of blood stream invasion even among those who never develop tuberculosis in a clinical form is attested by the common finding at autopsy of old encapsulated foci in the liver kidneys spleen lymph nodes and other tissues

The great variation in the number and severity of hematogenous lesions is related somewhat to the mass of the infecting dose, its physical suspension and the rate or repetition of its discharge Abrupt liberation from a liquefied caseous focus of myriads of tubercle bacilli which become finely dispersed in the blood may be the initiation of acute generalized miliary tuberculosis in contrast the escape of a single clump may result in only a single lesion at some distant point as in the kidney Numerous bacilli collected into a relatively few clumps and so deposited at various sites may produce the picture of subacute generalized tuberculosis in which many of the lesions are larger than miliary and become grossly caseous When bacilli are liberated in small doses at varying intervals of time the result is the establishment of hematogenous foci of varying age and chronicity as indicated by the

different sizes and different stages of caseation and healing In view of such manifold possibilities great variation must be expected and is observed in the clinical manifestations If the hemic invasion is not soon fatal (and usually it is not) lesions may progress where established and one result is isolated ulcerative tuberculosis of single organs In the kidney for instance the parenchyma may be destroyed and the infectious matter discharged through the ureter, may lead to invasion of the bladder Intermediate forms of more or less generalized or slowly developing hematogenous tuberculosis may be manifested by generalized lymphadenopathies exudates in one or more of the serous cavities and various forms of skeletal and visceral tuberculosis As stated the lungs are peculiarly open to attack because of their interposition between the smaller and greater circulations

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TUBERCULOSIS OF THE LUNGS

From the foregoing description it is seen that tubercle bacilli may gain access to the lungs in the inspired air through the blood stream or by direct extension from lesions in adjacent structures In fact infection may occur along several paths almost simultaneously since bacilli from the primary lesion acquired by inhalation infection may be liberated rather promptly into the lymphatics and speedily may reach the lungs again through the venous blood stream Pathologists have found in addition to the characteristic primary complex presumably hematogenous tubercles in the lungs of infants who have lived only several months Quite commonly however the primary lesions are arrested before much, if any hematogenous dissemination has occurred and this may be followed by permanent healing or by a period of latency during which the implanted infection is held in abeyance by enveloping *fibrosis* The latent period may last for many years after which old lesions in the lungs particularly those at the apices may become reactivated and go on to progressive ulcerative disease Similarly arrested lesions of the mediastinal lymph nodes or of some distant structure may become activated not only to cause local damage, but also to liberate tubercle bacilli freshly into the blood stream thus reinfecting the lungs Less commonly after an interval of latency, caseous lymphadenitis may ulcerate into a bronchus and through the resulting fistula discharge its highly infectious products into the lungs In adult life chronic pulmonary tuberculosis the most common form of the disease probably is initiated by one of these mechanisms especially the first mentioned more often than by any other Another alternative is exogenous reinfection by the renewed inhalation of tubercle bacilli and this is thought still by some to be the commonest

The *earliest evolution of chronic pulmonary tuberculosis* whatever may have been its origin is not often identified in the living patient Starting most often in late adolescence or early adult life the steps of progression are represented usually by direct extension of the lesion and by ulceration of its liquefied center, discharge of its contents into the bronchi and inhalation of the infectious pus into healthy alveoli immediately adjacent or in some more distant section (transbronchial or bronchogenic dissemination) These changes at first may be confined to microscopic areas Ulceration may be minute but the small quantity of liquefied matter liberated may contain numerous tubercle bacilli which if lodged in healthy alveoli are likely to cause an acute limited exudative reaction bronchopneumonic in character Depending on its size this secondary lesion also may be occult or it may be visible by x ray examination It may be absorbed it may become temporarily latent or it may progress immediately As a rule progression involves a repetition of the same processes of peripheral extension central caseation liquefaction *ulceration* and bronchogenic extension There is a succession of such steps until the disease becomes clinically manifest While the essential mechanisms are almost constantly the same the way of their operation varies greatly Thus the steps may succeed each other quickly in a space of a few weeks or months or only after long intervals of apparent quiescence and partial healing one renewed attack may be mild and abortive another acute overwhelming and fatal As a rule each leaves some permanent damage

Some of the influences responsible for these variations may be understood easily A small productive epithelioid tubercle does not break down and ulcerate readily If so it is a slow process with the discharge of small quantities of bacilli leading commonly to very gradual extension of the disease into surrounding areas A small exudative lesion on the other hand tends to slough early into the bronchus and to discharge larger quantities of bacilli consequently causing more acute and pneumonic types of secondary lesions Not only the quantity but also the concentration of bacilli liberated through the ulcerous tract into the bronchial tree has an important modifying influence If the discharge is slight and bacilli are few the secondary lesions if any are more likely to be of an isolated nodular and productive character But if a tuberculous abscess containing 1 cc., more or less of liquid pus suddenly breaks into a bronchus the huge dose of organisms which then may gain access to surrounding alveoli causes a most intense acute pneumonic reaction Once the ulcer or cavity has formed the fluidity of the discharge helps to determine the likelihood and seriousness of secondary lesions A coherent mucopurulent mass passing through the bronchi usually is carried intact to the trachea and may be expectorated readily by coughing but thin fluid pus gravitates easily into the smaller air passages This physical factor alone accounts largely for the greater liability to acute extension of the disease during and after a hemorrhage The posture of the patient when infectious matter from a cavity is aspirated may help direct the flow and determine the site of new lesions This is illustrated by certain results of pulmonary hemorrhage during which the patient usually lies supine in bed the subsequent tuberculous pneumonia is found most often in the posterior and dependent parts of the lower lobes where the inhaled baciliferous blood gravitated Since during sleep or unconsciousness fluid matter tends to accumulate in pulmonary cavities and protective mechanisms like the cough reflex are less active there is reason to believe that transbronchial spread of infection often occurs as the patient changes his position allowing the pus to drain into connecting bronchi

The *degree of immunity* acquired during the previous course of the disease and inborn constitutional resistance have a decided influence Hypersensitivity with low immunity apparently makes for acute inflammatory pneumonic lesions, high immunity and resistance for chronic localized productive lesions Massive infection however, overwhelms high resistance

As pulmonary tuberculosis runs its varied course the pleura almost inevitably becomes involved The nature of the pleurisy depends greatly on the underlying parenchymal reaction varying from a mild local fibrinous and later fibrous process to an acute diffuse and serous inflammation In chronic pulmonary disease the infrequency of serious and fatal hematogenous dissemination as compared with the first infection in childhood is striking By contrast however the frequent ulceration of chronic pulmonary lesions results commonly not only in a spread through the bronchial system but also in contamination of the mucous surfaces of the respiratory and gastro intestinal tracts Serious complications from this mechanism are observed often as tuberculosis of the larynx and of the intestine less commonly lesions are found in the middle ear to which bacilli may be carried through the eustachian tube in the tongue in the lips or in the buccal or gingival mucosa

Clinical Course in Relation to the Pulmonary Lesions—Tuberculosis must be visualized as a moving dynamic process and symptoms must be recognized as having a definite relationship to the changing lesions otherwise a satisfactory understanding of the disease can hardly be acquired Individual patients vary in their toleration of the effects of the disease Sensitive highly strung people are more aware of minor disturbances while the rugged and phlegmatic may not be conscious of mischief until the disease is far advanced The symptoms of toxemia are principally general and depend on the rate and degree of absorption of toxic products from the pulmonary lesions into the lymph and blood streams Localized toxic effects such as neurotropic manifestations are less conspicuous clinically

Profound toxemia seldom is manifest until the early lesions have ulcerated and discharged their contents giving rise to sec-

ondary extensions If however the toxic and liquefied necrotic centers of lesions are expectorated without incidental transbronchial spread of the infection general symptoms may abate This explains certain clinical disparities such as a patient gaining weight and experiencing a diminution of fever while pulmonary cavities are enlarging Ordinarily, toxemia lessens sooner than the local symptoms but this depends on the patient s activity When he is quiet circulatory interchange between the lesion and the tissue fluids is less than it is when he is exercising strenuously Manifest toxemia usually subsides before the pulmonary lesions become fibrosed Consequently constitutional symptoms are unreliable as indicators of the degree or rate of healing Local symptoms are related mainly to the effects of ulceration of pulmonary lesions Cough and expectoration then are due to the discharge of mucopurulent and purulent matter Similarly hemorrhage is seldom observed except in the presence of ulceration and excavation Pain may antedate these local symptoms if the pleura becomes involved early

While the *earliest discoverable lesion* in the lungs is usually of an exudative bronchopneumonic character there may be little or no manifest toxemia from it Several successive bronchogenic extensions may occur before the effect is sufficient to be subjectively apparent It is for this reason that patients usually do not become wholly aware of symptoms of pulmonary tuberculosis until it has progressed beyond the stage of excavation From this point the disease may come into the open so to speak and may be easily recognized as it runs the course of an acute or chronic disease with many intermediate gradations

Acute tuberculous pneumonia with its stormy clinical manifestations developing more often in the young than in the aged and more often in Negroes than in whites usually is initiated by the discharge of enormous numbers of bacilli from a cavity near the summit of the lung occasionally from a caseous lymph node which has ulcerated into the trachea or bronchus The reaction to such a mass of infection is prompt and marked by a rapid and widespread inflammatory exudation In other cases dissemination of the infection through the lungs may be slow and scanty and the secondary extensions may be only slight or *moderate, with a decided tendency to limitation and fibrosis* Local symptoms such as cough and expectoration may be mild and *the toxemia may be chronic* but not severe The progressive fibrosis of the lungs and the accompanying emphysema developing gradually *through many years may lead to* increasing respiratory difficulty, chronic malnutrition and impairment of working ability *Very commonly however the disease progresses* steadily or intermittently with greater intensity Each extension may give rise to *subacute constitutional symptoms* resembling those of grippe but each may be followed by prompt or gradual convalescence In such cases then, a combination of lesions of all phases may be seen such as a contracted scar at an apex a cavity below this and areas of bronchopneumonia elsewhere In the long standing cases the history and the morphologic pattern of the lesions as depicted in the x ray film may enable one by inference to judge their mode of development In summary, then it may be said that the severity of the secondary extensions from the early lesions their repetition and the intervals of time between them are the factors fundamentally determining the clinical course In time practically all progressive pulmonary tuberculosis becomes bilateral because of the facility of spread through the bronchial system In some cases bilateralization occurs promptly after the first ulceration The characteristic direction of spread is from above downward but it is not rare to identify an early infiltration in a lower lobe with secondary extensions from this toward the apex

The lungs commonly participate in *disseminated hematogenous tuberculosis* and *may bear the large brunt of the attack* In the acute generalized miliary form the lungs are quickly and uniformly seeded with small tubercles which as a rule do not ulcerate because death intervenes If dissemination is of lesser intensity the lungs may be studded uniformly with a few or a moderate number of tubercles Since the patient may survive then for considerable time perhaps years further local evolution of the lesions may occur Cavities may *develop in one* lung or simultaneously in both and from

this time on the course may be that of bronchogenic extension Occasionally the infection of the lungs through the hematogenous route is very mild although widespread The tubercles then may organize with little or no ulceration giving rise to a form of chronic pulmonary fibrosis and emphysema which eventually may be manifested chiefly by symptoms of functional respiratory impairment

Onset of Pulmonary Tuberculosis—As indicated in the preceding paragraphs the mode of onset varies greatly according to the sensitiveness of the patient and the behavior of the pulmonary lesions Commonly the first manifestations lag behind the actual appearance of the lesions and this *subclinical interval* may be short or long

Acute tuberculous pneumonia may produce the first clinical symptoms This form is uncommon although not rare being observed most often in young people in Negroes and in debilitated old people A preexisting excavating lesion is almost always present but the patient may not have been impressed with the mild symptoms caused by it The acute attack may appear to be precipitated by exposure to inclement weather by a common cold by severe sunburn by a hemoptysis or by some trivial influence The patient may experience chilliness prostration pain in the chest and fever usually moderate but sometimes severe and sudden The fever may rise quickly to 104° or 105° F and the pulse rate to 100 or more per minute The breathing is quickened at first (twenty to thirty respirations per minute) later becoming labored and more rapid as the lungs become further engorged it is seldom noisy or grunting A feeling of congestion in the chest increases and the lips and extremities become slightly or moderately cyanotic The cough may not be severe at first and may be productive of only a few cubic centimeters of mucopurulent sputum daily later larger quantities of a greenish yellow purulent character appear Unless hemoptysis occurred just before the onset the sputum usually is not bloody Herpes labialis is rare The leukocytes of the blood usually range between 12 000 and 18 000 per cu mm seldom above 20 000 The polymorphonuclear neutrophils seldom exceed 80 per cent of the total and usually fall short of this Because of the type of onset and the signs of lobar or lobular consolidation the picture may resemble closely that of a pneumococcic infection (see Differential Diagnosis) Subsequently however the longer course, the bacteriologic findings and the excavating nature of the lesions prove the true nature of the disease The patient may die within four to twelve weeks but in some cases the course settles down to a subacute or chronic pace

More often the onset is attended by *grippe like symptoms* such as fever weakness fatigue and mild aching in the muscles which subside after a week or several weeks perhaps to recur at intervals when the patient again undertakes exertion In other cases and this is very common there is an insidious unexplained slow loss of weight increasing fatigue and impairment of staying powers under ordinary conditions of work or activity These symptoms continue for weeks or months before the patient is aware of serious difficulty, then he may find an afternoon fever of a fraction of a degree to several degrees which has probably been present longer than he realized The usual rest does not restore his energies he finds his efficiency impaired and he is puzzled by his inability to concentrate on his work Others are disturbed by some particular constitutional symptoms such as *sweating* at night *amenorrhea* or *anorexia* and *indigestion* Under any of these conditions it is learned usually that the patient previously has had some *cough* and *expectoration* or at least a clearing of the throat in the morning Sometimes he will report that there has been a little blood in the sputum at irregular intervals In other instances *hemoptysis* may be the initial symptom so far as the patient is subjectively aware and this may consist only of a few spots or streaks of blood in the sputum or free and profuse bleeding He may find a small amount of blood accumulated in his throat upon awakening in the morning *Pleurisy* may be the outstanding initial symptom The pulmonary lesions may have been quiescent and the secondary pleural invasion may produce an acute fibrinous or serofibrinous inflammation with characteristic onset of acute pain in the chest aggravated by breathing fever prostration and dyspnea if the fluid ac

cumulates rapidly Much less often the first symptoms are related to a perforation of the pleura and the development of acute *pneumothorax* pain in the chest may be sudden and tearing and the dyspnea so acute that the patient collapses Following this, tuberculous or mixed infection empyema may develop Other tuberculous lesions closely or remotely related to the pulmonary focus may cause initial symptoms Hoarseness, dryness and tickling in the throat or other symptoms of acute or chronic *laryngitis* may be the first to arrest attention Acute *perianal abscess* or *fistula in ano* likewise may dominate the picture and first impress the patient

A patient does not sense relationships between symptoms of various kinds, consequently those which he describes as initial often are found to be secondary and sometimes quite remote After he has learned the true nature of his disease and some of its peculiarities he may be able to recall from the past significant episodes which had been entirely forgotten (See also the descriptions of pulmonary manifestations under generalized Lymphohematogenous Forms of Tuberculosis)

Symptoms of Pulmonary Tuberculosis —*Fever* —The fever of tuberculosis one of the commonest manifestations of toxemia is usually well tolerated by the patient It is not unusual to find him with a temperature of 103° to 105° F stating that he feels well except perhaps for some associated flushing and sweating Some even feel exhilarated or buoyed up others are more disturbed and complain of the unpleasant warmth Usually the temperature is found normal or subnormal in the morning the rectal reading sometimes being as low as 96.5° or 97° F and there may be considerable prostration and weakness The normal point may be reached late in the morning or about midday, after which the temperature begins to ascend Between four and eight P M it reaches its height which in acute cases may be 105° or 106° F More commonly in subacute or mild cases it ranges up to two or three degrees above normal In most cases a low or moderate fever recurs each afternoon or evening for some days or weeks and in the advanced case this may continue for many months During grippelike episodes the temperature may rise to 103° or 104° F daily for a week or so then gradually subside by lysis until it is normal after several weeks In acute tuberculous pneumonia often in pleurisy with effusion and sometimes in the presence of other complications the fever is hectic and temperature swings from 97° or 98° F in the morning to 104° F or 106° F in the afternoon for some days and within a lower range for many weeks In advanced chronic cases there is sometimes a reversal of the temperature curve with a high rise in the early morning In the incipient stages or during the early reactivation of old lesions slight afternoon fever may occur upon unusual exertion but this quickly disappears with rest and the patient may be entirely unaware of it unless a routine recording is made

Chilliness is sometimes a complaint associated with fever of 103° to 105° F, especially if this appears suddenly but ordinarily the patient has no such experience In fact the absence of chills at the onset and afterward is sometimes a point of value in differential diagnosis Likewise the patient seldom develops herpes labialis and if this occurs it is explained usually by some intercurrent acute respiratory infection

Sweating is not a feature of early tuberculosis and is not often a symptom except in the febrile and exhausted states Then it occurs usually at the time of the temperature rise and immediately afterward In some cases in which there is extensive excavation of the lungs and secondary suppurative infection the sweats are drenching and prostrating

Malaise lassitude and *fatigue* are the most common symptoms of tuberculous toxemia At first they are noticed toward the end of the day s activity when the patient may eschew his usual diversions or interests in order to get additional rest If he is the type to disregard such mild symptoms he may become irritable grouchy and impatient However the symptoms are not always unpleasant and may be evidenced only as an urge to rest and sleep If the toxemia increases its effects become manifest earlier in the day and the patient may even notice that on awaking his vigor and energy are not restored In progressive disease the languor grows finally into a profound weak

ness and exhaustion Nevertheless there may be little of the discomfort restlessness and mental depression which frequently characterize toxemias of other kinds

Loss of weight and impairment of tissue tone is also common At the true onset there may be no loss and a few patients even report gaining when their disease is first discovered The loss is usually gradual at first and may amount to only four or five pounds during several months Young people may fail merely to gain at the expected rate During acute and febrile phases the nutrition suffers much more rapidly and pronouncedly During tuberculous pneumonia for instance thirty to fifty pounds may be lost by a formerly robust person in six or eight weeks The impairment is first at the expense of the fat but later there may be wasting of the skeletal muscles and some atrophy of the skin The parenchymatous organs are more resistant but may undergo degenerative changes in chronic advanced stages of the disease

Cardiocirculatory instability is also a usual symptom and may persist long after the temperature becomes normal The customary manifestation is tachycardia the cardiac rate is regular and accelerated to 80 or 90 per minute during the early phases later even more After exertion or excitement the quickened rate does not subside as soon as might be expected The pulse is soft and the systolic blood pressure may be low frequently 90 to 100 mm Hg The circulatory tone may be poor and the patient may complain of clamminess and coldness of the hands or feet the nails may be bluish Clubbing of the digits may never develop and only in advanced complicated cases is it occasionally extreme Malar flushing and other local thermic disturbances are related to fever and vagosympathetic reflexes Except for the lowering of tone and the accelerated rate the cardiac function usually continues normal throughout the patient s illness In advanced fibroid forms of pulmonary disease however the progressive reduction of the pulmonary capillary and alveolar bed gives rise to increasing dyspnea and cyanosis and imposes an increasing burden on the right heart which occasionally may dilate and fail (cor pulmonale)

Pallor and *secondary anemia* may be pronounced symptoms in the advanced stages particularly if there is associated intestinal tuberculosis or amyloidosis In the earlier stages however anemia is usually only slight

Digestive symptoms of a vague character are frequent due particularly to the toxemia Severe distress such as dysphagia is not observed unless there is extensive tuberculous involvement of the larynx or pharynx Anorexia, manifested as an indifference to food or a capriciousness of the appetite is frequent but usually corrects itself as the toxemia abates after which the patient even though confined to bed may eat heartily In protracted cases there may be a mild or moderate gastritis caused in part by the irritation of swallowed purulent discharges from the lungs The stomach is rarely involved by an actual tuberculous lesion Vomiting is unusual unless the patient has advanced disease of the lungs and a harassing cough In these cases the continued irritation and effort to raise the bronchial discharges especially in the mornings may induce nausea and vomiting and occasionally the patient may lose several meals during the day (emetic cough) Intestinal symptoms such as seizures of colicky pain and diarrhea alternating with constipation strongly suggest an ulcerative lesion in the bowel as a secondary complication

Menstruation may be delayed in a tuberculous girl and in older women may be irregular and scanty but as a rule this is observed *only after disease is well established* Amenorrhea is unusual except during the very febrile stages The *fertility* of tuberculous women is somewhat impaired and in the advanced stages of the disease spontaneous *abortion* is not uncommon A striking observation however is that chronically tuberculous women may bear a number of children There is little or no impairment of the sexual functions otherwise During the early and middle stages of the disease neither the *libido* nor *potentia coeundi* are appreciably reduced

Nervous and *psychic disturbances* are mild or entirely lacking In most of the early and moderately advanced and many of the far advanced cases there is no appreciable change and the patient s reactions are quite normal under the circumstances Later he

may become rather neurotic dependent introverted and depressed (Schultz) This mood, however, is usually surprisingly mild considering the discouragement which such a chronic illness often entails *Suicidal tendencies* or attempts are most uncommon Euphoria which once was considered to characterize tuberculosis is not often noticeable except during the late or terminal stages *Toxic psychoses* are very unusual

Dyspnea is not usually an early symptom Slightly or moderately accelerated respiration may be noticeable during the febrile periods or in more advanced fibroid cases in which there is a good deal of secondary emphysema Granulomatous or stenotic tuberculous lesions of the trachea or bronchi sometimes account for dyspnea Sudden or rapidly developing dyspnea is usually traceable to some complication such as ulceration of the pleura and pneumothorax or rapidly developing serous pleurisy

Cough is the most common local symptom and like others of this class, seldom develops until the pulmonary lesion has broken down and ulcerated into the bronchi In the earlier stages cough is most pronounced when the patient awakes in the morning and is due to irritation of the bronchial mucosa from the accumulated discharges Occasionally cough is attributed to a reflex from irritation of the pleura, and later it may be traced partly to tuberculous involvement of the larynx At first the symptom is usually slight and is quickly relieved after the small accumulation is cleared from the trachea and larynx Later especially if pulmonary excavation extends and the discharges increase the symptom may become very troublesome interfering with eating and sleeping Finally the patient may become exhausted from the persistent but ineffective attempts to clear the passages Tuberculosis of the larynx or of the trachea and bronchi in some cases becomes so severe that these symptoms predominate the cough may then be of a distressing stridulous and painful character

Expectoration—During the initial phases of the pulmonary infiltration there is seldom any expectoration except perhaps a little clear glary mucus Later however expectoration is a most common symptom Its quantity and frequency are variable Only a few particles of mucopus may be brought up in the morning by clearing the throat or a few coughs, gradually this may increase In other cases expectoration starts more *abruptly* and may soon amount to 1 ounce or so in a day In any case with progressive pulmonary excavation, the quantity usually increases until 2 or 3 ounces are produced each day, mainly in the morning In advanced cases 10 or 12 ounces may be brought up daily, particularly after secondary infection of cavities has occurred The sputum is not foul except in the unusual case in which secondary anaerobic infection develops in the bronchi or pulmonary cavities When expectoration is slight the flecks of pus are seen in the clear mucus In caseous pneumonic cases, particularly at the start of excavation the sputum is purulent and of a greenish yellow color but later this usually becomes yellow and the admixture of mucus is noted In more chronic cases the mucopus is of a coherent, sometimes tenacious character The sputum on standing retains its homogeneous mucopurulent character and does not separate into layers The quantity and the character of the expectoration reflect to some extent the changes occurring in the pulmonary lesions A daily production of 2 or 3 ounces of purulent green matter speaks for a caseous pneumonic liquefying lesion A change to yellowish more mucoid sputum suggests a subsidence of the ulcerative process indicated further by a diminution of the amount and a continuing decrease of the purulent element Sudden and marked variations in the quantity of the sputum may be due to bronchial occlusion or to the rupture into the lung of a localized fluid collection in the pleura

Hemoptysis—Blood spitting occurs in more than one half of all cases of pulmonary tuberculosis As a rule the quantity is small consisting of streaking spotting or pinkishness of the sputum in the mornings but copious bleeding is not rare Hemoptysis usually is due to the ulceration or weakening and rupture of the walls of the vessels in tuberculous cavities Infrequently in chronic healed cases it may be traced to the mechanical rupture of superficial vessels in the walls of distorted bronchi An ulcerative lesion in the trachea or bronchus also is an infrequent cause As a rule the symptom

is obviously not an indication of early disease Bleeding may start at any time during the day or night but has been observed more frequently in the early hours of the morning Exceptionally it is induced by a violent straining effort or by trauma Staining or streaking of the sputum may occur without other sequels but in other cases is a precursor of more copious hemoptyses Frank hemoptyses however appear most often without forewarning and the patient may be awakened with a salty taste in the mouth or in the course of his work may notice a warmth welling into his throat In a minority of cases there is a feeling of congestion in the chest for a few days before the bleeding Because of such an experience previously an occasional patient is able to predict the hemoptysis In women there may be a definite relationship with menstruation and a few have recurrent hemoptyses monthly During the bleeding the patient may notice boiling or bubbling sounds in his chest localized to one side or to the center The blood may be raised easily or may flow so freely as to cause severe choking coughing and gagging

Immediately fatal hemoptyses occur only in a small minority of the cases usually of long standing fibroid cavernous tuberculosis in which vascular granulation and connective tissue have proliferated in the cavity walls a vessel may undergo gradual aneurysmal dilatation (Rasmussen) until it finally gives way The patient s lungs are quickly inundated with blood in which he drowns within a few minutes Fatalities in cases in which the amount of blood lost does not seem to be an adequate explanation have been ascribed to spasm of the glottis or reflex stimulation of the respiratory center through the autonomic nervous system As a rule however a single hemoptysis amounts to only several ounces occasionally to 10 or 12 ounces The bleeding is then usually arrested by the deposition of a clot at the site of the vascular rupture Dark clots may be expectorated for several days sometimes in the form of bronchial casts This may be the end of it but there may be a few or many recurrences at intervals of hours days or longer periods Then the loss of blood may cause secondary anemia The patient may become nervous and frightened or may go into mild shock with fearfulness pallor coldness of the extremities tachycardia and weakness sometimes sweating Vomiting may occur soon after especially if the patient has swallowed much blood Within a day or two there may be a rise in temperature of several degrees usually traceable to the aspiration of blood into the lower lobes of the lungs The inflammatory reaction may be mild and fleeting but often continues if tubercle bacilli have been carried into previously healthy alveoli Such *posthemorrhagic tuberculous pneumonia* then may be acutely progressive and cause the patient's death within four to eight weeks Rarely the hemoptysis occurs at the moment of a pleural perforation and pneumothorax when most of the blood extravasated from the cavity may accumulate in the pleural space

Pain in the chest is usually a symptom of inflamed pleura It may be an early complaint therefore if the initial pulmonary infiltration is situated close beneath the pleura facilitating such secondary extension The pain may be slight dull and recurrent or acute sharp and stabbing and may be aggravated by respiratory effort Usually it is localized fairly closely over the site of the pleural irritation but may be referred to the hypochondrium and to the trapezius ridge in case the diaphragmatic pleura is involved Acute pain does not persist as a rule for more than a few days but hyperesthesia of the skin in the areas of intercostal nerve reference may continue a few days longer In cases associated with chronic adhesive pleurisy a dulness heaviness soreness and aching of the side is a very common complaint and is particularly noticeable during fatigue and during cold damp weather Such sensations may be noticeable for many years after all activity of the lesions has subsided and the patient is sometimes relieved by the assurance that these are healing pains Mild retrosternal distress is complained of by emphysematous patients who are dyspneic and by patients with acute pneumonic tuberculosis A sudden stabbing pain in one side or behind the sternum followed immediately by shortness of breath and other manifestations is usually indicative of collapse of the lung and acute pneumothorax

Wheezing and *stridulous breathing* is

occasionally a complaint in cases of cavernous tuberculosis, less often in others The wheezing may be noticeable behind the sternum but more often is localized to one side of the chest and is due usually to distortions or stenoses of the bronchus or trachea caused by tuberculous ulceration, granulomas or cicatrices Rarely the trachea becomes so filled with granulations that suffocative attacks may occur In old standing fibroid cases wheezing may be referable to catarrhal accumulations in distorted bronchial tubes

Hoarseness may be the result of temporary congestion of the larynx from incessant coughing Persistent hoarseness dryness and tickling of the throat are caused often by laryngeal tuberculosis

Symptoms of Extrapulmonary Lesions.—Since the majority of patients with advanced pulmonary tuberculosis in time develop one or more lesions in the larynx intestine or other parts of the respiratory or alimentary passages clinical manifestations may be referable in small or large part to such complications A febrile exacerbation may be due to the onset of serous pleurisy which may not assert itself at once in any other way Huskiness of the voice in the morning may be the first evidence of tuberculous laryngitis while the feeling of aural fulness without pain and the development of slight deafness may herald tuberculous otitis media Lagging of the appetite and failure to gain weight at the expected rate in a patient whose pulmonary lesion is doing well may be the first inkling of ulcerative intestinal tuberculosis while the complaint of a tender hemorrhoid may in fact turn out to be a tuberculous perianal abscess A sore spot on the tongue which fails to disappear in a few days may be a tuberculous ulcer Headache persisting for a few days or more may be the only forewarning of tuberculous meningitis

Physical and X Ray Examination in Pulmonary Tuberculosis.—The examination of a patient for pulmonary tuberculosis should be thorough and complete Signs discovered in the chest may be relatively slight and inconclusive and the finding of some secondary lesion may give the most important clue to the diagnosis Through the various channels of systemic infection associated lesions may originate at any time and may be easily overlooked if the examination is cursory and limited Similarly, the systemic effects of the toxemia must be sought for and evaluated before the diagnosis can be said to be complete The classical steps of the physical survey, *i e* inspection, palpation, percussion and auscultation should be carried out with the patient stripped so that all accessible information may be obtained The patient should be made to feel at ease and should be carefully instructed to cooperate fully, particularly during auscultation of the lungs Likewise x ray examination should be carried out with the approved technic Fluoroscopy is useful and sufficient to visualize changes in respiratory mechanics and gross densities in the lungs which may be due to tuberculous lesions However the greater accuracy of the roentgenogram must be appreciated, particularly in detecting early lesions

Physical Examination of the Patient with Limited or Early Pulmonary Tuberculosis—The lesion while small or only moderately advanced may be of an early exudative nature or longer standing and fibroid In the case of a relatively early lesion physical examination reveals no superficial abnormalities or perhaps only slight evidence of anemia and loss of weight The temperature may be found normal or elevated a fraction of a degree to several degrees and the pulse may be slow or moderately accelerated Careful examination of the chest may not reveal abnormal signs or one may detect definite changes such as slight dulness bronchovesicular breathing and a few persistent crepitant or moderately coarse rales Rales alone may be found in an area scarcely more than 1 or 2 cm in diameter The roentgenogram as a rule reveals evidence of the lesion more precisely as a soft cloudy mottling often associated with small honeycombed areas of rarefaction or larger round zones of similar translucency which represent cavities It must be repeated that the early infiltration which has not yet ulcerated frequently does not produce abnormal physical signs but the x ray almost always shows the characteristic shadows Very infrequently in the case of a small tuberculous lesion the roentgenogram is negative or indeterminate while definite rales may be heard in a given spot

Oblique roentgenographic views or other special views then may reveal the mottling or rarefaction which in the customary postero anterior view was concealed by the interposed density of the heart or some other structure These evidences of the lesions are usually disclosed in the upper third of one lung not infrequently beneath the level of the clavicle but sometimes exclusively above it Signs of similar or different intensity and variety may be detected sometimes in both lungs These may be located on one side in the upper third and at the apex of the opposite lung or there may be other variations such as apical signs on one side and basal signs in either one of the lower lobes In a few cases the signs are limited to the middle or lower part of the interscapular region on one side occasionally even below this level In some the original apical lesion is so slight as to give no definite signs either by physical or x ray examination while the obviously secondary lesions are easily detected

Long standing and *fibroid lesions* may betray their presence through the changes due to retraction and shrinkage of the fibrous tissue Thus a rather limited depression of the clavicular fossae on one side slight or moderate atrophy of the muscles in this region limitation of motion of the ribs and deflection of the trachea give the main clue to the long duration of the lesion Isolated nodular fibrotic or calcified lesions such as those of the primary complex usually are not detected by physical examination but cast characteristic dense sharply circumscribed shadows in the roentgenogram

Physical and X Ray Signs of Advanced Lesions in Pulmonary Tuberculosis—There is no limit to the variety of signs which may be produced by tuberculous lesions which have passed the early phases If the disease remains confined chiefly to one lung this may be converted into a fibrous shrunken mass with a variety of secondary effects such as flattening and immobilization of the hemithorax atrophy of the muscles and skin on this side inequality of the pupils from involvement of the sympathetic ganglia flushing of one cheek from a similar cause dilated superficial venules of the skin of the chest marked deflection of the trachea and retraction of the heart The roentgenogram may show a shrunken and opaque lung and the retractions associated with it while physical examination may reveal dulness to flatness bronchial and amphoric breathing post tussic suction widely distributed rales and many other classical signs In the case of advanced bilateral fibroid nodular tuberculosis secondary emphysema may be conspicuous and the physical signs of this together with few rales may leave one in doubt until the roentgenogram shows that typical distribution of nodular and streaky shadows throughout both lung fields

Extensive bronchopneumonic or pneumonic lesions which have not existed long enough to produce such secondary changes give rise most constantly to widely distributed rales which vary from the crepitant quality in the early stages of infiltration to moderately coarse bubbling and consonating rales after the lesions have caseated and undergone liquefaction and ulceration With these are discovered varying signs of solidification and excavation depending on the concentration of the lesions in a given lobe and their state of degeneration Physical signs then may be more informative than the roentgenogram since in the latter the opacity may be so complete that detailed structure can no longer be made out Smaller bronchopneumonic lesions however are usually depicted more faithfully by roentgenographic than by physical signs In all these situations the findings may be associated with or modified by changes in the pleura or other adjacent structures A large pleural effusion may obscure pulmonary lesions while more chronic pleural changes may be well revealed by peripheral densities and retractions which stand out in contrast with the air bearing lung

Complete examination of the body may bring to light changes outside the thorax also Thus the discovery of an inflammatory thickening of one vocal cord of a phlyctenule in the conjunctiva of a nodule in the epididymis or of a fistula in ano may be most important factors in constructing the complete picture of the disease

Tuberculin Tests—The tissues of the tuberculous patient with few exceptions react with inflammation upon contact with products of the tubercle bacillus such as

tuberculin Many methods of application have been used for diagnostic purposes, and tuberculin has been introduced into the eye, and upon, into, and beneath the skin The tests now employed most frequently are the cutaneous intracutaneous and percutaneous The *cutaneous test* (von Pirquet) is made by lightly scarifying the skin of the volar surface of the forearm and applying on this a drop of pure Old Tuberculin (O T) The *intracutaneous test* (Mantoux) is made by injecting 0 1 cc of a measured dilution of tuberculin into the superficial layers of the skin creating a wheal Old Tuberculin or the purified protein derivative (Seibert's P P D) may be used, in terms of Old Tuberculin the initial test dose in sick patients is not more than 0 01 mg while in apparently healthy subjects it is usually 0 1 mg By graduated steps allowing an interval of four or five days to elapse subsequent tests may be done with stronger doses (ten times the previous strength) in order to detect slight hypersensitiveness but the dose is usually not carried beyond 1 0 mg O T A reaction is indicated by induration of the cutaneous tissues which may be appreciated by palpation and an area of redness varying from one to several centimeters in diameter at the point of inoculation In severe reactions a vesicle may form and occasionally there may be slight necrosis of the tissues associated perhaps with the pink streaks of lymphangitis extending up the forearm and palpable slightly tender nodes in the axilla The *percutaneous* or *patch test* is performed by applying to the skin a strip of adhesive tape on which a piece of gauze saturated with dried tuberculin is attached The reaction is represented by a red papular and occasionally slightly vesicular eruption at the point of application The patch test is said to approximate in accuracy the Mantoux test using 0 1 mg O T it is not very dependable when applied to a very dry skin The local tuberculin reaction may be apparent within twenty four hours but the test is not considered negative until seventy two hours have elapsed In addition to the local reaction there may be a constitutional reaction indicated by malaise and fever, also a focal reaction may be demonstrated by increased inflammation about existing tuberculous lesions Constitutional and focal reactions particularly the latter are to be avoided since lesions may be aggravated in this way A reaction is interpreted as evidence that the patient has been infected and harbors a tuberculous lesion somewhere in his body However the test does not determine whether the lesion is active or healed and has no bearing on the clinical status or indications for treatment The reaction may be depressed or absent (1) if the dose of tuberculin is too small (2) if existing tuberculous lesions are thoroughly healed and calcified (3) in the presence of severe acute attacks of measles and influenza, (4) during the latter months of pregnancy (5) in some terminal cases of tuberculosis In some of these situations however, large doses of tuberculin may elicit a reaction If the patient is not very sick a negative test in the presence of gross lesions in the lungs or elsewhere is presumptive evidence that these are not tuberculous

Laboratory Findings in Pulmonary Tuberculosis—*Sputum*—Proper collection and examination of the sputum is most important There may be no sputum if the pulmonary lesion has not ulcerated Even after ulceration has occurred the quantity of discharge may be so small that the patient is not aware of it and unconsciously may swallow it In this case the patient is carefully instructed to collect in a suitable container any slight discharge collecting in the throat particularly in the mornings If he is unsuccessful in producing a specimen lavage of the fasting stomach in the morning using a clean technic may recover in the washings a few particles of pus which then should be stained and examined microscopically or the whole specimen may be centrifuged and concentrated before the examination Organisms may also be found in the feces

Ordinarily the patient with a pulmonary cavity will be able to collect mucopus upon awakening in the morning and this is the specimen needed Occasionally bloody specimens or the blood from a hemoptysis will be suitable for examination While a great many elements may be searched for such as elastic fibers various types of cells secondary organisms and albumin these have only subsidiary value unless some special point is to be determined The most impor

tant necessities are an estimate of the character of the sputum and an effort to detect tubercle bacilli in it The sputum should be measured by volume or weight for each twenty four hours The character is noted as to appearance consistency possible layering and odor

Tubercle bacilli are detected by selecting mucopurulent particles smearing and fixing these on a glass slide staining by the Ziehl Neelsen method or some modification of it decolorizing with acid counterstaining and discovering on microscopic examination organisms which have retained the original dye In a recent modification carbolauramine is substituted for carbolfuchsin as the acid fast stain the tubercle bacillus is then discerned by the fluorescence microscope Such acid fast bacilli from the sputum are with rare exceptions tubercle bacilli Since this examination is so important in diagnosis it must be remembered that if the organisms are scarce in the sputum or are greatly diluted by the quantity of the latter examination of the smear may be negative In such cases therefore 2 to 4 ounces of the sputum are collected during the space of a few days if necessary and concentrated by centrifugation after chemical digestion The sediment is then stained to determine the presence of acid fast organisms Even then if there are only a few tubercle bacilli they may escape notice and it may be necessary to investigate further by inoculation of the collected sediment into guinea pigs or upon suitable culture media Perfection of the latter has partly displaced guinea pig inoculation Many comparative studies have been made and Loesch and Petrik report that in cases of pulmonary tuberculosis tubercle bacilli were discovered by culture in 24 per cent of the sputum specimens which were found negative on routine microscopic examination of a single smear or of the sediment collected after concentration With such exhaustive methods more than 90 per cent of all patients with active disease are found to show tubercle bacilli in the sputum and practically 100 per cent of those with pulmonary cavities *

Blood —In the early stages of pulmonary tuberculosis the erythrocytes and hemoglobin of the blood may remain unchanged later there may be evidence of secondary hypochromic anemia Similarly the leukocytes may not be changed in the early stages As activity continues and lesions progress the total leukocyte count may increase This may amount to 7000 or 8000 per cubic millimeter in the moderately active case and in acute tuberculous pneumonia may rise to 15 000 or more it is most exceptional however to observe a count as high as 20 000 Associated with the rise in the total count an increase of polymorphonuclear neutrophils and of monocytes may be noted together with a relative decrease of lymphocytes The Schilling count may reveal a shift to the left Later as the disease regresses and heals the cytologic picture may return to normal These changes parallel those of the pulmonary lesions fairly closely but there are certain discrepancies to be noted Thus during the early progression of the pulmonary lesion there may be no change detected in the leukocytic picture In fibroid cases the white cell count may deviate slightly or moderately from normal even though the patient is able to undertake a certain amount of activity with safety Various cytologic formulas have been suggested for estimating the trend and prognosis of tuberculosis These may be of value especially when set down in series during intervals of time The Medlar index (neutrophil–lymphocyte ratio with assigned values for abnormalities in monocytic percentages and in total leukocyte counts) is preferred by some Boissevain however finds the total neutrophile count is ample as an index

The *sedimentation rate* of the erythrocytes is accelerated in practically all phases of progressive febrile tuberculosis varying from a slight degree in the mildy progressive cases to a very marked one in highly febrile stages The sedimentation rate has no specific value diagnostically but is particularly useful in helping to determine the activity of the lesions Its reliability in this respect must be accepted with certain qualifications since the rate may be entirely within normal limits during the initial phases of the early pulmonary lesion in more advanced progressive cases when the patient is kept

* The techniques of sputum examination are described in a booklet "Diagnostic Standards" which may be obtained from the National Tuberculosis Association 1790 Broadway New York City

quietly at rest in bed and in old fibroid cases even though a pulmonary cavity may still be present

The *tuberculosis complement fixation test* is positive in most cases of pulmonary tuberculosis but also in many persons who have healed lesions and have never suffered from the disease in a clinical sense The test has not been found of great value in following the course of the disease Many other serologic tests have been devised, most of them of a nonspecific nature which show variations according to the activity of the tuberculous lesions However they are secondary in importance to accurate information of the clinical behavior the roentgenographic changes, and the character and content of the sputum Similarly in advanced cases disturbances in the balance of the mineral salts of blood of certain enzymes such as lipase and of vitamins may be demonstrated These changes are nonspecific are not of diagnostic help and as a rule do not yield many suggestions for treatment Recently, by means of electrophoresis Seibert and Nelson have found abnormal values for the serum proteins which seem to parallel the clinical course of human tuberculosis The conspicuous changes were a decrease in albumin, a rise in the gamma and alpha globulins and the appearance of an unknown (x) component

Urine—In febrile tuberculosis the urine commonly shows slight traces of albumin Protein loss through the kidney may become marked after amyloid changes have occurred From the results of animal experimentation it has been suggested by some that tubercle bacilli free in the blood stream may be excreted through the intact and normal kidney and then may be discovered in the urine (excretory bacilluria) In human beings however experience indicates that this must be a rare happening and the discovery of bacilluria is taken as presumptive evidence of a tuberculous lesion in the urinary tract or in the genital organs The discovery of pus cells and an abnormal number of erythrocytes or persistent albuminuria in a patient with pulmonary tuberculosis should always lead to a further investigation for the presence of a renal lesion

Pleural Fluid—In some cases of pulmonary tuberculosis complicated by a pleural effusion the discovery of tubercle bacilli in the aspirated fluid may verify the diagnosis when this evidence is lacking on account of negative tests of the sputum

Basal Metabolic Rate—In afebrile cases of pulmonary tuberculosis this is found to be normal unless there is some independent cause for variation In febrile cases the rate is elevated according to the degree of fever

Respiratory Function—In the presence of limited lesions the respiratory function is not materially disturbed Later it may be impaired because of the extent of the involvement, the shrinkage of fibrous tissue and the associated distortion of blood vessels Such an effect may be aggravated also by pleural adhesions and by retractions of the heart or constrictions in the pericardium The nature and extent of the changes may be estimated by functional tests designed to measure pulmonary ventilation diffusion and circulation

Diagnosis of Pulmonary Tuberculosis—Tuberculosis should be considered as a possible cause (*a*) in any patient who presents vague symptoms of loss of weight malaise and easy fatigue particularly when this is associated with persistent cough (*b*) in any patient particularly a young person who has recurrent or prolonged attacks simulating grippe or influenza (*c*) in any patient who has atypical or unresolved pneumonia (*d*) in any patient who has cough and expectoration persisting for more than several weeks even though there may be little or no impairment of the general condition (*e*) in any patient who spits blood (*f*) in any patient who has pleurisy, especially with effusion (*g*) in any patient with a persistent unexplained fever (*h*) in any patient with other mild or obscure lesions such as persistent lymphadenopathy fistula in ano and chronic laryngitis giving rise to chronic hoarseness The diagnosis then depends particularly upon physical x ray and laboratory examinations Under such circumstances the finding of a lesion usually in the upper one half of the lung which gives the characteristic x ray appearance of an infiltration or fibrosis with or without cavity and with or without demonstrable physical signs such as rales warrants the presumptive diagnosis of tuberculosis If there is no demonstrable cavity and no sputum the



Fig 29—Infiltration of mixed exudative and productive character in the upper third of the right lung

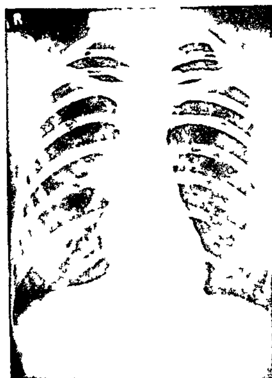


Fig 30—Early infiltrate in the lower lobe of the right lung at the level of the seventh rib posteriorly Tuberculosis of the right bronchopulmonary lymph nodes

diagnosis is confirmed by a period of observation during which the lesion persists or gradually changes If excavation is demonstrated or suggested by the other examinations the diagnosis may be verified by the finding of tubercle bacilli in the sputum The failure to find bacilli in a case in which there is moderate or fairly copious mucopurulent sputum weighs heavily against the diagnosis of tuberculosis The finding of tubercle bacilli in the discharges or material secured from other lesions such as pleural effusion

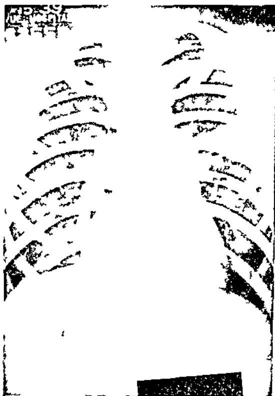


Fig 31—Tuberculous cavity in th right lower lobe at the level of the eighth rib posteriorly Exudative infiltrate in the middle of the left lung representing a bronchogenic extension from the cavity

or pus from a tuberculous fistula strongly suggests that the pulmonary lesions are also tuberculous The finding of rales in the upper one third of the chest in a case in which the roentgenogram shows no parenchymal change and in which the sputum test is negative leaves the diagnosis in doubt and raises the question whether the lesion is nontuberculous The finding of physical and x ray signs exclusively in the lower one half of the chest does not rule out tuberculosis as a cause but if in addition there

is mucopurulent sputum devoid of tubercle bacilli tuberculosis as a rule can be excluded

Modern methods of *tuberculosis case finding* among apparently healthy people afford another approach These surveys are usually conducted by routine x ray examination of the chest, with or without a preliminary tuberculin test In about 2 per cent of apparently healthy people densities are discovered in the lungs which may be tuberculous The lesions are usually in the upper one half of the chest often confined to one lung and may be of a caseous or fibrous character Discovery of such a shadow in the roentgenogram necessitates a complete history of the case complete physical examination, and study of the sputum These tests together with the necessary period of observation usually confirm the tuberculous nature of these lesions

Differential Diagnosis of Pulmonary Tuberculosis—The approach to differential diagnosis varies according to the presenting findings Thorough and careful study of the case usually enables one to arrive at a definite conclusion

In a patient who develops unexplained fever and who is discovered to have an exudative infiltrative lesion of the lung which has not ulcerated distinction often has to be made between early tuberculosis and *simple bronchopneumonia* especially if the lesion is confined to an upper lobe Demonstrably rapid changes in the lesions within a few days or a week and failure to find tubercle bacilli usually identify bronchopneumonia as such, while the failure of the lesion to clear in the expected time favors tuberculosis Occasionally acute caseous pneumonia occupying a large part of the lobe or lung may be confused with *pneumococcic lobar pneumonia* and the confusion may be increased by the finding of pneumococci of a higher type in the sputum While in a rare case of tuberculous pneumonia the leukocytes of the blood may rise to 20 000 the count seldom attains the height commonly seen in lobar pneumonia nor is there often such a pronounced relative increase of the polymorphonuclear neutrophils Since caseous pneumonia usually represents an acute confluent bronchopneumonic extension from a tuberculous cavity tubercle bacilli will be found on careful search of the sputum which, as a rule is not rusty although it may be bloody In caseous pneumonia the signs of cavity may be detected on physical and x ray examinations If not immediately the diagnosis usually can be made in the space of a relatively few days Acute bronchopneumonia due to organisms such as *streptococcus* or *anaerobic bacteria* which commonly goes on to abscess formation may be confusing because of the pattern of the pulmonary lesions simulating tuberculosis The acute onset often with chills the leukocytosis the finding of an abscess or cavity and the failure to demonstrate tubercle bacilli in the sputum are presumptive evidence against the tuberculous nature of the disease while a great predominance of other specific organisms may give the real clue One must be certain, however that common pyogenic organisms are not merely contaminants from the mouth

Foulness of the sputum shortly after the acute onset of the disease always speaks for *putrid lung abscess* In long standing cases of chronic lung abscess a cavity or fibrotic lesion may be discovered in the upper part of one lung and this may give rise to suggestive symptoms such as hemoptysis The history of onset particularly the history of fetid expectoration and the failure to demonstrate tubercle bacilli usually indicate the diagnosis

When tuberculosis is suspected as the cause of a *protracted and obscure fever* the failure to find a pulmonary lesion is presumptive evidence against this diagnosis but it may be necessary still to rule out tuberculosis of other organs The same is true in any chronic debilitated state in which tuberculosis may be suspected

Bronchiectasis not infrequently must be differentiated in patients who give a history of chronic cough possibly with bloody sputum The lesion is usually in the lower lobes but occasionally is apical Rales may be heard but the roentgenogram fails to show the typical tuberculous infiltration and excavation and instead there may only be strandlike densities suggesting interstitial or peribronchial fibrosis This and the absence of tubercle bacilli from the sputum suggest bronchiectasis which may be verified by the use of bronchography with iodized oil

Cancer of the lung simulates tuberculosis because of the chronic cough, expectoration of pus and blood febrile episodes and gradual wasting Physical and x ray findings are more likely to be those of an invasive growth or of suppurative pneumonia secondary to the bronchial occlusion The failure to find tubercle bacilli in the purulent sputum is most important Bronchoscopy the biopsy of a superficial metastatic lesion in a lymph node or the finding of other internal metastases may be diagnostic

Pulmonary fibrosis and *emphysema* may have to be differentiated because of symptoms and because tuberculosis particularly the chronic hematogenous form sometimes is a cause Chronic cough occasional blood spitting and increasing weakness may be particularly suggestive In tuberculosis the fibrous changes are usually associated with calcifications identified by x ray Extrapulmonary lesions may also be found especially in the lymphatic system or in the abdomen The history of some other possible cause such as chronic paranasal sinusitis or exposure to injurious dust may give the proper clue In silicosis the nodular noncalcareous roentgenographic appearance of the lesions evenly distributed in both lungs particularly in the central portions is characteristic Association of the tuberculosis with silicosis a not infrequent finding may be suspected when there are confluent roentgenographic shadows in addition to nodular ones

Mycoses may produce changes simulating tuberculosis but these are unusual The lesions may be of a subacute bronchopneumonic or chronic granulomatous and fibrous nature and the pattern in the roentgenogram may simulate tuberculosis closely even to cavity formation In a patient suffering with a chronic cough expectoration and general ill health failure to demonstrate tubercle bacilli and the finding of specific fungi in the sputum by microscopic or cultural examinations may settle the diagnosis other tests used include the serum antibody titer skin sensitivity tests and virulence of the organisms for animals It is important to know whether there has been an opportunity for infection with fungi and whether there have been systemic lesions Fungi may be found in the sputum as contaminants from the mouth but these are usually scarce and nonpathogenic

Pulmonary lesions secondary to cardiac disease sometimes create a confusing picture The hemoptysis of mitral stenosis may be misleading at first because of the finding of rales and roentgenographic changes suggesting fibrosis and infiltration of the parenchyma Demonstration of the cardiac lesion the failure to demonstrate a cavity the lack of sputum containing tubercle bacilli and the distribution character and behavior of the lesions lead correctly to the conclusion that these are due to secondary fibrosis from congestion and stasis to infarction or to edema A pleural effusion clouding the picture may be found related to the same cause Rarely a pulmonary *infarct* may become secondarily infected and break down to form an abscess simulating a tuberculous cavity

Suppurative lesions in other structures which may become connected with the lungs must be distinguished Thus chronic pleural empyema which has ruptured into the lung may cause many symptoms common to pulmonary tuberculosis and the same may be said of chronic hepatic or subphrenic abscess which has perforated through the diaphragm into the lung A searching history of previous illnesses and operations and failure to demonstrate tubercle bacilli in the sputum usually eliminate tuberculosis

Unusual conditions such as Hodgkin s lymphoblastoma invading the lung from the mediastinum esophagotracheal fistula dermoid or parasitic cysts which have ruptured into the lung and aortic aneurysm producing bronchial stenosis by pressure may necessitate ruling out tuberculosis because of the symptoms of chronic pulmonary disease The clinical history the failure to find tubercle bacilli and the demonstration of other lesions especially in the mediastinum exclude tuberculosis as a rule and suggest the proper diagnosis

Prognosis of Pulmonary Tuberculosis —Because of the many factors which influence the course of the disease the prognosis is difficult Important factors which should always be taken into consideration include the extent and character of the lesions the clinical symptoms the age sex and color of the patient the presence of complications

and certain environmental conditions There is a definite correlation between the *extent of the lesions* and the ultimate prognosis Early or limited lesions without cavity formation almost always do well under suitable treatment in such cases the life expectancy, as indicated by studies such as those conducted by Trudeau Sanatorium is equal almost to that of groups of similar age in the general population The more extensive the pulmonary lesions the greater is the future hazard Patients with far advanced cavitary disease do not survive as a rule, more than two to five years unless some special treatment changes the course About one third of the patients with moderately advanced disease are reported dead within five years The *character of the lesion* is of great and sometimes paramount importance Lesions of a productive nodular character tend to run an indolent course and are more readily controlled by treatment the tendency to excavation is less, while delimitation by fibrosis is customary Exudative bronchopneumonic lesions may be resolved rather rapidly but there is almost always an unresolved caseous center and the predominating trend is for this to liquefy and slough into the bronchial tree with secondary extensions into the healthy parenchyma The instability of these lesions is striking particularly during the first year or two after their discovery The *size and character of cavities* also has a prognostic bearing particularly since these are sources of infectious discharge which frequently is responsible for secondary lesions in the lungs larynx and intestine there is also a liability to hemorrhage Patients with cavities more than 2 cm in diameter which are not suitable for treatment by collapse therapy usually remain more or less disabled and most of them die within five years However a patient with a small fibroid cavity may survive for many years despite tubercle bacilli being constantly present in the sputum On the contrary a cavity recently developed in a caseous pneumonic lesion impairs the prognosis greatly because of the likelihood of rapid dissemination The *distribution or concentration of lesions* is significant A moderate number of small lesions scattered in isolated positions throughout the lung usually offers a better prognosis than if these were concentrated in one area where the likelihood of excavation would be great

Clinical symptoms measure in an approximate degree the patient s reaction to the infection Thus, a young girl who reacts with prolonged fever usually does badly while an older person with more tuberculosis but no fever may have a better prognosis Another guide is the amount and character of the *sputum* a patient who has only a small quantity, mucopurulent and coherent may live for years without extension of the disease On the contrary, a large amount of more liquid sputum favors early extension In either case the number of tubercle bacilli in a given quantity of sputum may be approximately the same Generally however the prognosis is better if tubercle bacilli are scarce, since this may be interpreted as evidence that the cavity walls are relatively clean and not undergoing active necrosis *Complications* may alter or actually determine the prognosis A patient with a small cavity and good prognosis may be changed within a few days following a hemorrhage into one with desperate acute tuberculous bronchopneumonia The same may be true when ulceration of the pleura pneumothorax and mixed infection empyema rapidly develop Other complications such as tuberculous laryngitis or tuberculous enteritis impair the prognosis somewhat but, unless these in themselves are severe and extensive they may heal with the pulmonary lesions Nontuberculous complications similarly may have an important influence Severe diabetes mellitus especially when this is difficult to control renders the outlook less favorable Acute pulmonary complications such as putrid abscess may cause rapid extension of the disease People with arteriosclerosis usually do not have good resistance Active syphilis tends to impair the prognosis

The *age* of the patient is of great prognostic significance Tuberculosis acquired during infancy or early childhood is of serious portent as indicated by the careful studies of Wallgren Miriam Brailey and Edith M Lincoln Adolescence is a serious time with relation to pulmonary disease Young tuberculous girls have notoriously unstable lesions and the mortality is relatively high there is a similar trend some

what less striking among young boys Women past thirty have a relatively good prognosis while men in the older age groups have a higher mortality *Constitutional and racial characteristics* may be given some weight Under equal conditions Negroes do not survive tuberculosis as well as most whites Patients of poor constitutional make-up seem to react poorly although exceptions are numerous particularly when proper environment is provided

Controllable factors which have the most definite relation to prognosis are *early diagnosis and prompt and proper treatment* If the lesion is detected as an early infiltration which has not yet excavated and treatment is instituted without delay the prospect is that at any age and in almost any type of patient recovery will occur and a sufficient prolongation of treatment will avoid relapse

Treatment of Pulmonary Tuberculosis—Until recent years tuberculosis was seldom diagnosed until the patient developed symptoms clearly indicating treatment The perfection of diagnostic methods particularly the use of the x ray and the development of modern case finding surveys has altered and complicated the situation considerably Therefore the first task of the physician after discovering a tuberculous lesion is to determine its clinical status and whether treatment is needed Whatever the diagnostic approach may have been the patients generally may be grouped into (1) those who obviously require treatment (2) those who obviously do not require treatment and (3) those who are of uncertain status and may be observed for a time to determine the need of treatment The third group includes patients who may be observed (*a*) while they continue their usual activities and (*b*) those whose status is so uncertain that observation should be carried out under the conditions of bed rest

Those Needing Treatment—The first group comprises all patients with clinical symptoms such as fever malaise fatigue cough and expectoration and the spitting of blood It includes also patients with recently developed lesions or lesions the instability of which is proved or inferred it is to be emphasized particularly that these still may be in the subclinical phase producing few or no symptoms One of the commonest errors in practice is the postponement of treatment or minimization of its need until clear-cut symptoms have developed meaning usually that the physician fails to appreciate the significance of an early infiltrate until this has broken down into a cavity under his very eyes Also proper measures should be instituted promptly for the patient whose disease previously became arrested under treatment and who now shows indications of relapse such as the appearance of a positive sputum x ray evidence of a change in the lesions or undue constitutional symptoms such as great loss of weight

Those Not Needing Treatment.—The second group includes patients in whom the roentgenogram reveals the calcified residues of the primary complex which may have been acquired in childhood and has long since healed The important exception is the finding of large and multiple apparently calcified lesions often lymphatic in the chests of children or adolescent youths in these cases the occurrence of pulmonary tuberculosis later is considerably greater than it is in the general group of young people who react to the tuberculin test but do not harbor such large foci usually these are only partly calcified partly caseous often bacilliferous Healthy adults found to have obviously fibrotic scars at the pulmonary apices do not require treatment The same is true of adults who show the scars of old pleurisy or healed extrapulmonary lesions Periodic examination yearly is indicated because apparently healed tuberculous lesions frequently contain tubercle bacilli which may be responsible for extensions or relapses under the vicissitudes of ordinary living

Those Requiring Observation—Group 3*a* includes adults who have lesions of uncertain stability or apparently well healed lesions involving more than the pulmonary apices and who have vague symptoms of fatigue loss of weight or malaise In such patients particularly if they are more than thirty years of age these lesions usually do not change rapidly and observation may show that the symptoms are referable to some other cause As a rule it is best for the patient to continue working provided he follows a prescribed daily routine in order that his health may be evaluated accurately

The temperature and pulse should be recorded in the late afternoon and evening during the period of observation and all symptoms, even slight should be reported, specimens of sputum should be submitted for examination, even if the bronchial discharge is very scanty The leukocyte count and the erythrocyte sedimentation rate are particularly valuable supplements when estimated at intervals of one to several weeks, to show slight grades of toxemia and any change in the trend Roentgenograms of the chest should be made at least once every month Usually it may be decided within several months whether there is any instability of the disease necessitating treatment or whether the patient may continue at work under supervision at intervals of several months

Group 3*b* includes, mainly, patients less than twenty five years of age with lesions of doubtful status and those more than this age in whom competent fibrosis of the lesions is not readily demonstrable Any adolescent youth or any adult in his early twenties showing a limited pulmonary lesion which in the roentgenogram casts a soft poorly circumscribed shadow, should be observed under conditions of bed rest since such lesions are usually of recent origin unstable and potentially dangerous The absence of symptoms is no criterion that treatment is not needed Somewhat greater latitude may be allowed the older patient the roentgenographic appearance is the best means of deciding whether fibrosis is sufficient or whether the patient had better be in bed pending determination of this point During the period of observation definite symptoms may assert themselves though this is unusual, and reliance must be placed mainly on serial roentgenographic examinations In adolescent youths roentgenograms should be made for comparison at intervals of at least two weeks sooner if there are definite or doubtful symptoms in older persons the interval may be two to four weeks In either case after a period of stability is proved the examination should be repeated monthly and this is continued until the status of the patient is clearly determined Instability of the lesion whether progressive or regressive is an indication for treatment and the younger the patient the more strict this should be Likewise, searching microscopic and cultural examinations of the sputum and gastric washings should be made for tubercle bacilli, the presence of which indicates the need of treatment But—let it be stressed—negative findings do not mean necessarily that the lesion is not dangerous and not in need of treatment

Principles of Treatment—Since there is no known specific cure for tuberculosis treatment rests entirely on a recognition of the factors contributing to the resistance of the patient and the adjustment of the daily routine so that these may operate most effectively Many of the factors can be only suspected or indirectly identified experience, however, has proved their dependability as a basis of treatment The chief principle is *rest* which may vary from strict rest in bed to a combination of rest periods and regulated exercise The effect of rest is both local and general Diminution of the respiratory rate and amplitude implies lessened motion of the lung which is known to favor healing of tuberculous lesions Another effect which may be even more important than this is the diminution of the circulatory rate and of the volume of blood passing through the lungs A result of these mechanisms is lessened circulatory interchange between the lesion and the lymph and blood streams and diminished diffusion of toxins, manifested by the subsidence of symptoms such as fever and tachycardia The same mechanisms explain the observation that patients placed at rest often experience a prompt diminution in the expectoration and consequently of the cough while the sputum changes from a greenish purulent to a more mucoid yellowish consistency Rest also relieves certain local strains which at times may precipitate serious accidents such as hemorrhage or rupture of a weakened pleura Similarly the quieting of respiratory movements helps to avoid the inhalation into healthy parts of the lung of purulent discharges issuing from tuberculous cavities

Clinical experiences suggest that resistance is promoted by good physiologic tone of the alimentary and cardiocirculatory functions and by other less obvious vegetative responses Alterations of vascular tone and capillary permeability seem clearly to account for certain clinical phenomena such

as hemoptysis during menstruation and perhaps the exudative nature of lesions developing in the presence of uncontrolled diabetes Well maintained vascular tone may be assumed therefore to be a feature of good resistance helping to avoid harmful inflammatory reactions about old tuberculous lesions and to hold in abeyance such tendencies in recent lesions until fibrous encapsulation has had time to develop Bodily rest particularly if this is understood as complete physical relaxation and mental quiet undoubtedly contributes to the physiologic tone which always is an important and often the most important factor in recovery To think of rest only in its mechanical relation to respiratory motion is to take too narrow a view of the principles of successful treatment

While the immediate necessities of the case must be recognized and met treatment to be successful ultimately also requires planning according to a visualization of the future potentialities of the disease in each case this ability is acquired only by sound experience Potentialities may be quite remote and failure to comprehend them may not betray itself immediately but to the detriment of the patient only after a lapse of months or years To recognize and observe this principle therefore is one of the most responsible functions of the physician In a pulmonary cavity he visualizes the possible source of a pulmonary hemorrhage In a recently disseminated tuberculous bronchopneumonia he sees the potentiality of early resolution or early caseation and excavation In an early infiltration he senses the alternative of relatively rapid resolution of the peripheral exudate and subsequent fibrous encapsulation of the caseous residue or liquefaction and sloughing of the latter to mark the first of successive steps toward advanced bronchogenic tuberculosis He appreciates further that a long period of treatment to assure complete and durable encapsulation of the remains of the early infiltration is far superior in its ultimate results to the compromise of permitting the patient to return to work as soon as symptoms subside and then after relapse and cavity formation collapsing the lung by artificial pneumothorax As stated early diagnosis is the best guarantee of a good prognosis but the vital bridge between diagnosis and lasting recovery is the quality of treatment

Under rest treatment with the proper kind of clinical observation the limitations of the patient s resistance may be determined and special procedures may be adopted when needed Excepting unusually pressing situations time for this determination should be allowed It is not generally a good principle to proceed immediately upon making the diagnosis to some form of collapse therapy on the theory that mechanical pulmonary factors are the sole agencies in healing

Guides and Checks in Treatment—In order to apply the principles of treatment most effectively the observation of the patient should be systematic As a rule relatively simple clinical data supplemented by periodic examination of the sputum roentgenography of the chest and study of the blood suffice The temperature is recorded during the day at least every four hours occasionally two hourly observations may be desirable for short periods and it may be necessary sometimes to obtain nocturnal records also Unless there is some valid objection rectal temperatures should be taken since they are more dependable The pulse rate is recorded each time the temperature is taken it is well to remember that the pulse may continue unstable after the temperature remains normal and therefore may be considered a more sensitive indicator of toxemia or other disturbances The body weight is recorded every two weeks unless the patient is too sick Note is made of the patient s appearance his general feeling and of his vegetative functions A tendency to sweating coldness of the extremities irritability and digestive disturbances may be significant Likewise attention is paid to special symptoms such as pain in the chest hoarseness or diarrhea These may be indicators of some underlying change which can be determined by the proper examination

The sputum is collected during each twenty four hours in a disposable container so that the amount and character may be estimated If tubercle bacilli are found at the outset later examinations at intervals of a month may show some change such

as a diminution in the bacillary output, which with a diminution in the quantity of expectoration may be significant If bacilli are not found at the start such repeated examinations are indicated to verify the diagnosis and to detect early this evidence of an ulcerative process in the lung At the start the sedimentation rate of the erythrocytes and a complete total and differential count of the leukocytes should be recorded The milder the symptoms and the closer the approach to quiescence and arrest of the disease, the more likely are these estimations to be valuable Then a series of observations at intervals of several weeks or months may help to determine the trend of the disease and particularly the degree of stability attained under treatment

While repeated physical examination is indispensable its value is variable and it is not to be relied upon to detect early and slight changes in pulmonary lesions For this purpose the roentgenogram is much more dependable How often this examination should be made depends on the behavior of the case In young people with exudative and unstable lesions roentgenograms at intervals of a week show not infrequently definite extensions or regressions which are most important to recognize in old fibroid cases, few or no changes may be shown during long periods The interval must be determined therefore according to one s judgment of the potentialities at the start of treatment and for six months afterward this examination should be made at least once a month At any time an unexplained occurrence such as fever severe pain or breathlessness necessitates prompt investigation by physical examination and roentgenography or fluoroscopy The latter may be the most convenient and rapid way of determining certain changes such as pneumothorax

Application of Treatment—Treatment is carefully planned according to the existing and potential needs of the patient taking into consideration the personal social economic and environmental situations Modifications from a standard method are often indicated thus a patient discovered with advanced bilateral tuberculosis may be judged to have very little prospect of recovery and he may be left relatively undisturbed in his home since the important consideration is his personal comfort and contentment On the contrary, the benefits of treatment to be expected in an early case in a young person are so great as to justify radical dislocation of the domestic routine and heavy sacrifices by the patient and his family

The *place of treatment* is usually the first consideration While in hopelessly advanced cases the patient s comfort may be favored by his remaining in the home the possible hazard of infecting others in the household, particularly young children should be carefully investigated before sanctioning this Similarly it should be determined whether the responsibilities of the care of a chronic invalid may not impose excessive burdens on other members of the family possibly endangering their future health or security Under such circumstances it may be wise to provide for the patient in a sanatorium or nursing home A patient with moderately advanced or advanced cavitary disease particularly if there are serious symptoms such as hemoptysis or complications requiring investigation should not remain at home but is best treated in a nearby hospital If this is not accessible readily it may be necessary to tide him through the acute episode until it is safe to transport him to a sanatorium At the start young people with relatively early pulmonary tuberculosis usually require strict rest in the hospital or sanatorium where they may receive the education and instruction so vital to their complete and lasting recovery They profit by seeing patients with more advanced disease and are impressed with the wisdom of following medical advice in order to avoid this misfortune In the home the lack of companions who have similar objectives makes it more difficult for young people to take the cure Older seasoned patients who previously have undergone sanatorium treatment and now have relapsed sometimes do better at home where another adult is able to provide the necessary nursing and dietary care

CLIMATE may have a virtue as a part of the treatment but this depends on the individual situation Climate alone is of little value and its overestimation in times past deprived many a patient of his chance of recovery Other conditions being met a young person with recently developed and

not too advanced tuberculosis usually does well in a cool invigorating climate and he tolerates cold dry winters extremely well His physiologic tone seems to be promoted Old poorly nourished patients do best in a mild balmy climate High altitudes have a doubtful value except for the purity coolness and stimulating quality of the moving air they are contraindicated for the dyspneic patient with fibroid tuberculosis and emphysema Warm dry climates and a moderate altitude such as in southern Arizona are conducive to relaxation and rest during the winter for many patients with moderately advanced and chronic disease Whatever the merits of a given climate may be they may be far outweighed by economic or social considerations An indigent patient is best treated in a public hospital near his home and a patient with limited means usually responds best in a nearby locale where the expense is not great and he may be visited by his family at intervals Since the establishment of hospitals in many cities of the United States and other countries ample proof has been provided that skilled treatment in such well conducted institutions is the important element in recovery so much the better if these institutions are situated in the suburbs where there is at least a simulation of the quiet countryside

INSTITUTION OF TREATMENT —The *time for treatment* to be instituted is usually at once This is never disputed in the case with severe or alarming symptoms Postponement for a short time may be permitted in the adult patient with chronic tuberculosis obviously of long standing when this concession is necessary to permit settling affairs in business or at home The necessity of prompt treatment of the disease in adolescent youths or young adults however is too frequently underestimated Here the delay of a few days or several weeks may spell the difference between uninterrupted healing and early excavation and extension of the lesions The physician needs strong convictions and persuasive powers in this situation since the patient usually is unconvinced because of the lack of symptoms There are few circumstances in which the physician is more justified in taking an uncompromising stand to induce the patient and his family to take advantage of this rare chance for lasting and complete cure He is justified further in describing vividly the probable alternative

SCHEME OF TREATMENT —This is best illustrated by considering the patient with moderately advanced febrile tuberculosis As a rule it is best for him to understand from the outset that treatment will be long and recovery slow since such proper advice may permit him to arrange his affairs wisely and deter him from expending his financial resources rapidly with the hope of getting a quick cure Explaining in a simple way the mechanism and rate of healing of lesions is more likely to win the cooperation and acquiescence of the patient and his family than rash promises which later lead to disappointment and loss of confidence in the physician The patient must know the nature of his disease and the sooner he accepts the diagnosis and adjusts to it the more successful is his treatment likely to be The behavior of symptoms is also explained so that while he may be watchful he will not become unduly apprehensive as these fluctuate from time to time If he is able to cultivate and preserve a calm patient and cheerful attitude his progress is unquestionably favored this of course is a large task for the young active enthusiastic and emotionally high strung person but youth is more adaptable than sclerotic senescence

The *plan of treatment* is adjusted to individual indications The patient with obviously hopeless disease is not required to conform to the same stringent routine as the one in whom recovery is anticipated Elderly people with long standing fibroid tuberculosis often tolerate mild physical exercise well and may even be helped by this they are not advised to remain in bed constantly unless there is some special symptom requiring it With such occasional exceptions all patients with active or potentially active tuberculosis who have a prospect of recovery are kept strictly in bed Mildness or complete absence of symptoms is not necessarily an indication that such rest may be omitted In fact strict bed rest has its greatest value in the case of a young person with recently developed tuberculosis who may have few or no symptoms Complete rest treatment

then is the best means of preventing advanced cavernous tuberculosis after the cavity has formed no treatment can be quite as effective as this

Strict bed rest means confinement to bed throughout the day and night the patient not being allowed to take any steps Occasionally, when the use of a bedpan is difficult, the commode may be substituted While the patient may change his position for comfort he is instructed that the degree of rest has a definite effect in accelerating recovery and that he should avoid unnecessary moving and restlessness Usually he may be allowed to sit up in bed and feed himself but if symptoms are acute or severe even this is denied and he must be fed by a nurse *Special postures* in bed may be favored with relation to the involved lung Lying on the affected side supported with sandbags or pillows lessens the motion of the lung on that side and may promote healing On the other hand if there is a basal cavity or if the bronchi are distorted or obstructed this position may favor the accumulation and stasis of exudate and secondary suppuration, the patient is then encouraged to change his position from time to time so as to promote drainage Brock and others report some success keeping the patient flat with the foot of the bed elevated 18 inches throughout the day and night and some patients report a diminution of the amount of expectoration when in this position Quietness of the patient and limitation of respiratory movement may sometimes be favored by keeping a bag of lead shot weighing from 2 to 5 or 6 pounds on the affected side of the chest Casts braces straps and other devices have occasionally been used to limit the motion of the affected hemithorax but simpler methods seem to be just as good if the patient cooperates

The *duration* of strict rest in bed depends on the symptoms and behavior of the pulmonary lesions Constitutional symptoms such as fever may disappear soon or late and at a more gradual pace the cough and expectoration may diminish and finally cease With this the sedimentation rate of the erythrocytes and the leukocyte count may return to normal All this is favorable but does not show necessarily that adequate and durable stabilization of the lesions has occurred yet Bed rest should be continued, therefore to allow time for fibrous organization to be well initiated In general, this requires from two or three months to a year or more depending on the extent and character of the lesions To be guided alone by the symptomatic response is usually to be deceived and the patient who leaves bed prematurely usually experiences a relapse immediately or after a period of apparently good health the "false recovery which Laennec described Sufficiently effective healing of the lesions is determined chiefly by periodic roentgenographic and bacteriologic examinations When cavities have shrunken and closed as indicated by roentgenographic changes and absence of tubercl bacilli from the sputum and when infiltrative lesions have reached a point of stability as indicated by a cessation of resolution and a sharpening of the outlines of the roentgenographic shadows the patient is well on the road to recovery and everything should be done to insure that this will continue Too much physical activity or loss of rest may cause renewed inflammation about the lesions caseous degeneration of their centers and the reopening of apparently healed cavities

Since stability is a relative quality, which may be constant under conditions of bed rest but unreliable under excessive exertion, rest is not discontinued abruptly but very gradually allowing the patient to undertake mild exertions increasing by slow steps At first he may sit in a chair for fifteen minutes a day and after a week or two this may be increased gradually Then he may take a few steps or walk slowly for five minutes daily for a week or two again increasing at intervals until at the end of several months he is sitting up several hours a day and walking for perhaps thirty minutes Using the checks and guides which have been described the kind and rate of exertion are regulated according to the response of the patient and its effect on his lesions In time the patient may be walking an hour or two a day or doing some light task such as writing weaving typing or tooling leather for three or four hours daily The time required for reaching this point varies from six months in an adult with a chronic limited lesion to a year in an adolescent girl with

a freshly developed pulmonary infiltration and to longer periods for the person with more advanced disease particularly if this has been bilateral caseous and cavernous In a good many advanced cases one can hope for nothing better than relative quiescence of the disease without complete healing of the cavities and the patient must accept chronic invalidism as his lot In these when quiescence has been approximated the routine of rest is relaxed and more consideration is given to the patient s comfort granting him reasonable indulgence

The *diet* should be varied and should contain in adequate amounts the elements which are now known to be necessary for the promotion of good general health There is no proved virtue in eating excessive amounts In some cases a low carbohydrate high protein diet may be beneficial Sandler and Berke have described the effects in a carefully controlled group of patients For most patients milk is easily digestible and particularly if they are undernourished a glassful may be drunk morning afternoon and night in addition to that taken with regular meals

Fresh air has always been considered an important feature of the treatment Sleeping out may be salutary for many patients particularly young ones but there is no virtue in a frigid temperature especially when rest is hindered by weight of bed clothing

The tonic effect of *sun baths* and *artificial heliotherapy* in carefully graded doses may be helpful after the pulmonary lesions have become well stabilized and fibrotic Deleterious effects have been observed in patients with active or exudative lesions particularly when sunburn has occurred and there seems to be a danger of precipitating hemoptyses with overdosage in such cases The tonic effect of *air baths* taken on a shaded porch may be appreciated also by some patients

Drugs may be used for their symptomatic effect None have been demonstrated to have an effective or specific influence on the course of human tuberculosis Gold compounds such as sanocrysin have been used widely with questionable or sometimes damaging results The same may be said for many chemotherapeutic agents vaccines and serums The striking antibacterial effects of the sulfonamide drugs have led logically to their trial in tuberculosis While the course of the disease in experimental animals seems at times to be retarded no such definite effects have thus far been demonstrated in patients

The treatment often has to be modified or supplemented on account of the existence of complications which usually are due to tuberculous lesions elsewhere in the body These are described in the paragraphs pertaining to the given lesions

Collapse Therapy —Perfection of mechanical therapy to bring about immobilization and collapse of the lung and the good results obtained in well selected cases necessitate considering the possible usefulness of these in every case Careful judgment is required since every measure of treatment has limitations complications and potentialities of harm if improperly used In the early case of minimal extent healing under the rest regimen alone is the rule and collapse of the lung is not usually necessary It has not been proved that healing of a non cavernous lesion is accelerated by this artificial means beyond the rate to be expected from simple rest Indeed following the principle of promoting the patient s general resistance by every possible means rest treatment is not omitted even though artificial collapse of the lung may be needed also In cavitary tuberculosis there are almost always secondary bronchogenic infiltrations the prognosis is less favorable and collapse therapy therefore is indicated more often The most striking effect of the procedure is the closure and healing of cavities when rest treatment alone offers little or no prospect of accomplishing this necessary end The important mechanisms are approximation of the walls of cavities lessening respiratory motion and slowing the circulation of blood and lymph continuing until the healing process has had time to become thoroughly established

Artificial pneumothorax is induced by injecting clean air in measured amounts from a special apparatus through a hollow needle into the pleural cavity Providing the lung is not adherent the introduction of air permits the lung to retract and collapse through its own elasticity the alveolar spaces and tuberculous cavities may collapse simulta

neously In the average case, however, the stiffness of the fibrotic cavity walls, the density of surrounding lesions or the presence of pleural adhesions interfere so that in ultimately successful cases three to six months are usually required before the cavity is completely closed and tubercle bacilli disappear from the sputum Barring complications the treatment is then continued for two to four or five years depending on the extent of the lesions, in order to insure good healing After this the lung is permitted to reexpand At first the treatment is carried out by insufflating air every two or three days and later as this is absorbed less rapidly through the pleural membrane every week or few weeks the pleural pressures always being registered on a manometer connected to the pneumothorax apparatus It s important to use aseptic technic to avoid infection of the pleura The effect is observed by frequent fluoroscopic examinations and by other guides The treatment is chosen and tried in any case of pulmonary tuberculosis in which one lung is involved with cavity and infiltrations, provided a reasonable period of rest treatment alone has proved ineffective or offers no prospect of adequacy The other lung often is affected but the lesion here should be slight limited, and preferably inactive or quiescent In more advanced cases pneumothorax sometimes is undertaken as a partial aid with the hope that other measures may also be used For the control of hemorrhage in cavernous cases it is usually effective provided adhesions do not interfere In a few cases in which both lungs are affected *bilateral pneumothorax* may be induced with benefit, but good eventual results are rather meager In predominantly unilateral disease artificial pneumothorax is sufficiently effective in about one third of the cases attempted in the remainder adhesions are so extensive as to defeat the purpose Sometimes these may be severed by Jacobaeus s *intrapleural pneumolysis* using a cautery guided under direct vision through the thoracoscope introduced between the ribs Complications are encountered frequently in artificial pneumothorax Air embolism may be avoided by careful technic in the Tuberculosis Service of Bellevue Hospital it has occurred only once in every 10 000 to 12 000 thoracenteses Serofibrinous pleurisy, usually tuberculous is a frequent complication (80 to 90 per cent of the cases) As a rule this is mild and the fluid may be absorbed spontaneously If chronic adhesions develop at the base of the lung and the pneumothorax may be lost Otherwise, the visceral pleura becomes organized and fibrotic, and the lung may fail to reexpand In a minority of cases the fluid becomes empyematous and the pleural disease chronic, amyloidosis then may be a result Pleural perforation and secondary mixed infection empyema occur occasionally, more often in the active caseous forms of pulmonary tuberculosis There are other less common complications

Pneumoperitoneum induced by insufflating air into the peritoneal cavity has been tried to raise the diaphragm and lessen its motion The results have not been impressive the peritoneum may be irritated by the air and the patient may be uncomfortable

Paralysis of the hemidiaphragm by interference with the phrenic nerve is accomplished by avulsion of the nerve or by crushing or cutting it along its course Crushing (phrenemphraxis) is now used since the nerve regenerates within six or eight months and the diaphragm resumes its function this is desirable, particularly if the procedure has proved ineffective Diaphragmatic paralysis has been found effective in a limited number of cases in which there is a round thin walled, somewhat recently developed pulmonary cavity situated in the lower or middle one third of the lung not attached to the chest wall by surface adhesions It has the disadvantage in some cases of interfering with the effectiveness of cough for eliminating discharges from the bronchi particularly if thoracoplasty must be undertaken later It may also cause mild gastric disturbances and some impairment of blood circulation and ventilation of healthy parts of the lung

When less drastic measures fail or offer little promise *thoracoplasty* may be indicated Sections of ribs are removed usually from above downward the number depending on the extent of the cavernous lesion Two or more operations may be required The ribs are removed subperiosteally and eventually they regenerate partially in the collapsed position This often results in ap-

proximation of the walls of the cavity and the release of tension so that enveloping fibrosis may be effective for healing The operation is indicated in well stabilized fibroid disease of one lung in which there is a cavity which has not healed or does not promise to heal under other treatment If lesions are present in the opposite lung they should be well arrested in more desperate cases active lesions in the latter may be controlled possibly by pneumothorax Bilateral thoracoplasty has been performed occasionally but the resulting limitation of respiratory function is usually great Thoracoplasty should not be delayed if pneumothorax proves ineffective which as a rule may be determined within several months The operation may also be indicated if pneumothorax is complicated by intractable tuberculous empyema Probably 5 to 10 per cent of tuberculous patients may be helped by thoracoplastic operation By designing the operation for the individual situation the results are usually favorable in well selected cases

Another operation is the separation of the parietal pleura from the ribs and collapse of underlying lung as the parietal pleura is stripped away over the lesions The resulting space has been filled with various substances such as wax fat or muscle in recent years air has been used (*extrapleural pneumothorax*)

Distortion or obstruction of bronchi leading into tuberculous cavities may hinder drainage and cause gas to collect under tension in the cavity Suction drainage by the Monaldi technic using a catheter inserted through the chest wall may then be beneficial Untoward complications are sometimes observed and thoracoplasty is eventually necessary in most of these cases

Tuberculous lobes and lungs have been successfully resected in a few clinics but the field of this procedure is necessarily very limited and remains to be clearly defined because of the anticipated hazards

Treatment of Special Symptoms — *Cough and expectoration* traceable usually to excavating lesions of the lungs are best controlled by rest treatment The patient is instructed to wait for the mucopus to be carried by ciliary action into the trachea or larynx when it may be raised easily by gentle clearing of the throat or by slight coughing this avoids the irritation and unnecessary respiratory motion caused by frequent and futile coughing In some far advanced cases, however these symptoms are rather incessant and it is necessary to give sedatives such as codeine sulfate ½ grain at intervals of three or four hours or longer so that the patient may get sufficient rest sometimes this may be supplemented with a hypnotic at night For the distressing cough of patients who have considerable bronchitis steam inhalations perhaps with the addition of some medication like creosote or tincture of benzoin may be alleviative Expectorant cough mixtures often cause a gastric upset and are to be avoided if possible In the early morning when the patient experiences difficulty in clearing out accumulated discharges a drink of hot water or hot lemonade may stimulate the flow When the exudate accumulates in large cavities coughing sometimes is reduced by having the patient assume a posture which facilitates drainage for fifteen to thirty minutes two or three times a day In the case of a basal cavity he may hang over the bed with his head down Keeping the foot of the bed elevated 15 to 18 inches may help to prevent stagnation of exudate in cavities In some cases the cough may be referable to tuberculous lesions of the larynx or trachea and bronchi and treatment should be directed to these

Hemoptysis consisting only of slight streaks or spots of blood in the sputum requires no special treatment save rest in bed Large hemorrhages are usually traceable to cavities in which blood vessels have been laid bare by the ulcerating process Treatment is designed to arrest the bleeding and to prevent a dissemination of the infection in the lungs by aspiration of contaminated blood The patient should be in bed and in order to restore calm and quiet he may be reassured justifiably that the bleeding will subside Violent coughing favors aspiration of the blood into healthy alveoli and if the patient is unable sufficiently to restrain the impulse codeine sulfate ¼–1 gr may be given hypodermically Morphine is seldom indicated and then only in small doses ⅛–⅙ gr Too much sedation depresses the reflexes unduly and may permit

the retention of clots in the bronchi, which is undesirable For a day or two after the initial hemoptysis, dark clots may be expelled or fresh bleeding may recur, usually in diminishing amount If the hemorrhages are large or frequently repeated especially in cases in which the disease is predominantly unilateral artificial pneumothorax is often indicated to relax the lung and with it the bleeding vessel, this, as a rule is effective Usually, however pneumothorax is postponed for a few days or longer until accumulated blood has been cleared from the air passages since this lessens the possibility of acute pneumonic reactions and serofibrinous pleurisy after the pneumothorax If pneumothorax fails other forms of collapse therapy may be considered in emergencies occasionally thoracoplasty or extrapleural pneumothorax is indicated without delay Diaphragmatic paralysis is less effective However most hemoptyses subside after the loss of a small or moderate amount of blood and collapse of the lung may then be determined according to the usual indications During and for a few days after the hemoptysis, the patient is given a soft or light diet according to his desires and it is not necessary usually to restrict this to fluids Blood may be swallowed and thereby excite nausea and vomiting If there is constipation a saline cathartic may be given The patient is encouraged to lie on the affected side but during the waking hours he may change his position from time to time since this aids in expelling clots of blood Sometimes the patient goes into mild shock during the hemoptysis This is treated by keeping him warm and giving him warm drinks and if necessary infusions of glucose in solution If there are small frequently recurrent bleedings transfusion of 200 to 300 cc of fresh blood may be helpful Numerous drugs such as atropine nitroglycerin horse serum and calcium have been given to control hemoptyses but these seldom prove efficacious since the coagulating properties of the blood are not disturbed When bleeding is continuous though slight intravenous injections of calcium gluconate sometimes seem to be helpful but the effect of such measures is always difficult to judge In certain cases the prothrombin content of the blood may be low the administration of vitamin K is thought by some to be helpful in such conditions

Dyspnea of sudden onset usually is due to acute pneumothorax or pleurisy and is treated accordingly In advanced fibroid cases the symptom may become aggravated during attacks of acute bronchitis or bronchopneumonia when oxygen therapy is indicated for relief

Pain in the chest is traceable most often to pleuritic involvement, strapping with adhesive plaster may give relief

Night sweats occur most often in advanced febrile cases and are relieved usually by rest in bed and proper nursing Drugs such as atropine or agaricin have little effect The patient should not be covered too heavily with bed clothes and the room should be airy and cool Alcohol rubs or baths before retiring are helpful After the sweat the clothing should be changed and patient should be given an alcohol rub

Secondary anemia is treated by a good general diet and, if necessary the addition of ferrous sulfate Often the most effective measure is the proper treatment of the complicating intestinal tuberculosis

Maintaining Arrest and Avoiding Relapse —In many advanced cases of tuberculosis the physician must recognize the impossibility of complete arrest of the disease and strive only to alleviate symptoms But when there is a prospect of returning the patient to useful life it is important to estimate when treatment has been sufficient to assure stability of the disease in the situations he is obliged to face later

According to the standards of the National Tuberculosis Association the disease is considered *arrested* when the lesions have remained apparently healed tubercle bacilli have not been demonstrable and the patient has been symptom free under conditions of moderate physical activity for at least six months Since the lesions still harbor viable tubercle bacilli and relapse is possible the gains are to be maintained and consolidated during the next several years Experience shows that if the patient goes through two years with continuing arrest the chance of relapse later is greatly minimized During this time close and systematic medical observation and advice are very important, as is the cooperation of the patient in follow

ing faithfully a prescribed daily routine In most successfully treated cases six months to a year of 'arrest should elapse before the patient returns to work During the interval as far as practicable his daily schedule of activity should be increased gradually until it approximates that which he expects to continue at work Patients who have followed light or sedentary occupations usually do best in returning to the same particularly if the employer is willing to make some concessions pending complete rehabilitation One-half day's work may be safe at first to be gradually increased during the following months or years Other patients often have to be educated for a new occupation since laborious work under unfavorable conditions is always to be interdicted Institutions like the Papworth Colony and Preston Hall in England the Altro Work Shop in New York City and the Potts Memorial Institute at Livingston N Y have been instrumental in rehabilitating many patients who could not return immediately to conditions of competitive employment but who responded well under sheltered conditions and the humane skilful supervision afforded in these places there is a great need for more of them If the patient is so unfortunate as to be obliged to return to his work and to resume his social and domestic responsibilities without this easy transition he is likely to become ill again and this is followed too often by his complete demoralization the disruption of his family and his dependence on public relief —a great waste in the long run

Since the diagnosis of tuberculosis usually is not made until the disease is advanced and treatment often is postponed or inadequately administered and since proper rehabilitation is not generally and scientifically provided fully 50 per cent of the patients treated in sanatoria have relapses after discharge The picture is entirely different when the disease is diagnosed in its incipiency treatment administered promptly and properly and after arrest a normal life is resumed gradually under skilled guidance most of these patients live a normal span of years and die of some other cause Avoidance of relapse therefore is contingent mostly upon fulfilling these conditions

Periodic medical supervision is indicated indefinitely after recovery At first the patient should be seen once a month and during this time he should be questioned about symptoms the sputum should be searched for tubercle bacilli and a roentgenogram should be made for comparison with those previously accumulated Continued good general health absence of tubercle bacilli and unchanging roentgenographic shadows (except perhaps for slight further contraction of the fibrotic lesions) permit as a rule continuation or expansion of the daily routine After three or four months the interval between examinations may be gradually lengthened but for the first two or three years the patient should be observed in this way every three to six months and afterward at least once a year The appearance of symptoms should always be the occasion for medical examination to determine the cause

J Burns Amberson Jr

TUBERCULOSIS IN CHILDREN

Certain peculiarities of tuberculosis in children deserve special mention In early infancy the disease may be of grave significance lymphohematogenous dissemination may occur ending fatally or leading to the establishment of multiple systemic lesions The latter may become destructive at once or after a short or protracted period of latency There is sound evidence that the avoidance of infection in early childhood goes far toward avoiding chronic tuberculosis in adulthood Between early childhood and adolescence there is relatively little danger of death from tuberculosis though infection may be acquired (See Figs 27 and 28)

The customary distribution of lesions following primary infection in childhood helps to direct diagnostic investigations While the important lesions are found most often in the chest these as a rule are not of the ulcerative excavating parenchymatous type The usual predominance in the mediastinal tracheobronchial and bronchopulmonary lymph nodes explains the failure to discover the lesions by physical examination unless they are extensive X ray examination therefore is just as important as or even more important than in later life Since

recently established lesions are more likely to be progressive the greater implications of the tuberculin test in children are obvious A positive test in an infant is synonymous with recent infection and with active and potentially serious disease and should arouse suspicion that there may be an active source case in the household While children may suffer occasionally from ulcerative tuberculosis of the lungs clinical manifestations are referable much more often to the caseous masses in the mediastinum or the lesions which have been disseminated from this source by way of the lymph and blood stream Consequently, the symptoms of a tuberculous mediastinal tumor are much more common in children as are secondary pulmonary effects resulting from pressures on the bronchi or ulcerations into them Similarly, one must be on the alert to detect systemic lesions varying from generalized miliary tuberculosis to isolated and perhaps latent lesions in various organs and tissues

Treatment —Treatment of the tuberculous infant is not very promising since uncontrollable factors like the size of the infecting dose of bacilli and the immediate inflammatory response of the lung and lymph nodes largely determine the fate of the victim The situation is in no way comparable to that of the adult whose life is threatened by the consequences of an excavating lesion in the lung which may be controlled by artificial pneumothorax In later childhood the greater tendency to spontaneous limitation of the infection becomes increasingly apparent Treatment then may be directed with greater promise to enhancing general resistance by a proper routine of rest and good nutrition, localized lesions may be treated with appropriate measures such as immobilization for a tuberculous joint collapse of a cavity bearing lung or excision of a tuberculous lymph node

The child with a positive tuberculin test but no demonstrable tuberculous lesion or only several isolated calcified lesions should have a roentgenogram of the chest once a year particularly as he approaches and enters adolescence but no other treatment is indicated unless a new lesion appears The child with demonstrable lesions obviously of recent origin and of a fresh inflammatory type should be treated just as an adult with an early pulmonary infiltration

J Burns Amberson Jr.

GENERALIZED LYMPHOHEMATOGENOUS FORMS OF TUBERCULOSIS

Acute Generalized Miliary Tuberculosis —The disease occurs most frequently in young children or infants and occasionally in adult life The patient may have been in perfectly good health previously or may have had some clinical or other demonstrable evidence of tuberculosis such as roentgenographic signs of mediastinal lymphadenitis The onset may be abrupt with chilliness prostration aching in the muscles headache and drowsiness or gradual with malaise weakness and fatigue for a period of a few days or a week before the patient becomes prostrated The temperature may rise at once to 103° or 104° F in the afternoons or attain this level gradually during a week or so Night sweats may be profuse the soft tissues waste rapidly and the patient is overcome by weakness Localizing symptoms depend on the predominant distribution of miliary tubercles Dyspnea and cyanosis may become pronounced because of the extensive and rapid invasion of the lungs but there is usually no cough or only a slight hacking In other cases peritoneal symptoms such as pain distention and constipation may predominate Effusions may accumulate in the serous cavities with the well known clinical manifestations of their presence if they are profuse The clinical course may resemble that of typhoid fever but the onset is usually more insidious in miliary tuberculosis rose spots do not appear and diarrhea is usually not a feature

Physical examination initially shows only the general effects of the toxemia After a week or more fleeting rales may be heard in the lungs later numerous and persisting fluid may be demonstrated occasionally in the pleura or peritoneum less often in the pericardium The spleen becomes palpable in only a minority of the cases Uncommon findings include superficial lymphadenopathy and tubercles in the ocular fundi The roentgenogram of the chest is indeterminate at

first but usually shows characteristic stippling of the pulmonary fields within a week or two The leukocyte count remains normal or becomes elevated to 15 000 or 20 000 seldom more Death occurs usually within six to eight weeks occasionally with meningeal involvement

Subacute Forms of Lymphohematogenous Tuberculosis —These likewise are observed most often in the early ages but occasionally also in adults particularly Negroes Tubercle bacilli enter the lymph and blood streams usually from a lymphatic focus perhaps at recurring intervals The number of lesions established in various organs is only moderate and since the patient does not die soon time is sufficient to permit further local development with degeneration or partial healing Many bacilli are picked up by the lymphatics and come to rest in various regional nodes The lungs are frequently involved the lesions being particularly prominent in the upper parts The spleen kidneys liver and serous membranes often participate

The variety of clinical manifestations is great but some are fairly constant The patient may have obscure fever which has persisted for days or weeks without other obvious symptoms except loss of weight malaise and fatigue In time peripheral lymphadenopathies may become apparent as in the auricular cervical axillary epitrochlear and inguinal regions A roentgenogram of the chest may show only widening of the upper mediastinum from the lymphatic lesions The spleen may become palpable within a few weeks or months Other patients with similar fever reveal evidence only of an effusion in the pleura peritoneum or perhaps in several or all of the serous cavities Still others may be found to have genito urinary tuberculosis and occasionally papulonecrotic tuberculides of the skin give the first clue to the identity of the fever Multiple lesions in the bones and joints and in the eye may be associated some may become ulcerous or fistulous

Probably a majority of these patients die within three to six months but a few survive longer and rather seldom one may live for many years harboring disseminated partly calcified lesions chiefly in the lymph nodes Progressive bilateral ulcerative pulmonary tuberculosis is often the predominant lesion toward the end

Latent and Chronic Forms of Lymphohematogenous Tuberculosis —It is not uncommon at autopsy to find tubercles originating obviously in lymphohematogenous dissemination of the infection perhaps many years before distributed in such structures as the spleen liver kidneys lungs and lymph nodes These may be small even microscopic gray tubercles isolated in fibrous capsules Others are represented by encapsulated round calcified nodules sometimes they are so discrete and nonspecific in appearance that they are mistaken for simple phleboliths Reichle and Work found such lesions in 20 1 per cent of 452 routine autopsies at the Cleveland City Hospital, and upon further investigation demonstrated that most of them were tubercles While these foci may never assume clinical significance they are latent depots from which local active disease may develop after weeks months or even many years

Chronic disseminated lymphohematogenous tuberculosis may be visualized as a stage between the subacute and the latent forms The chronic form may be due to the slow evolution of mild infection disseminated during or shortly after the development of the primary complex to the reactivation of old systemic lesions which may have remained latent for years or to renewed hematogenous infection from old foci which have become reactivated The character and distribution of the lesions may be manifold and in some cases one may see granulomatous and caseous lesions ulcers and fistulas in one or more joints in the lymphatic system skin eyes or in the abdomen or thorax Whether they are numerous few or single is largely a matter of chance depending on factors of infection resistance age and location of previous lesions Probably the most common clinical picture is mild chronic tuberculosis involving various lymph nodes possibly one or more of the serous surfaces and the lungs Mild exudative or plastic inflammations may appear and recur in the serous membranes and there may be slight or moderate recurrent swelling of lymph nodes which on roentgenographic examination appear partially calcified

Involvement of the lungs usually appears

as lightly distributed nodular, fibroid infiltration, most pronounced at the apices and at the hilar levels which later may be associated with varying degrees of interstitial fibrosis secondary emphysema and chronic adhesive pleurisy The symptoms usually are vague, the patient may be chronically undernourished and frail and may experience periods of low fever for weeks or months Later he may develop dyspnea and slight or mild cyanosis on account of the fibrosis and emphysema The cough if any is slight and hacking and there is only a little mucoid expectoration unless the pulmonary lesions go on to ulceration Recovery or improvement may take place slowly leaving behind scars and secondary changes which may be harmless or cause mechanical or functional disturbances On examination, the lungs reveal signs of emphysema, with no rales or only a few fine ones scattered mostly in the upper halves The roentgenogram however, usually discloses the suggestive finely nodular and strand like densities radiating from the hila particularly toward the apices and may also show the pleural thickening and signs of emphysema The discovery of other lesions in the skin kidney epididymis or elsewhere may help to establish the diagnosis In some of these cases especially in elderly males the chronic debility may raise the question of malignant disease with metastasis particularly if the pulmonary lesions are atypical and associated with a serous effusion in the pleura Tuberculosis is not an uncommon cause of such manifestations at this age and should always be considered

Tuberculosis of the Serous Membranes—Any of the serous membranes may become infected usually singly but sometimes in combination The pleura is most commonly involved secondly the peritoneum less often the pericardium The way of infection is by direct extension from some contiguous tuberculous lesion or by the blood or lymph streams The lesions appear as isolated tubercles or as fibrinous or serofibrinous inflammations The tubercles may be few and isolated or numerous and disseminated through the membrane Fibrinous changes usually are rather limited while serofibrinous inflammations involve the whole membrane which is edematous and red The serous exudate may be absorbed leaving behind a rough fibrinous coating of the serosa and fibrinous deposits may become partially or completely resolved As a rule, however, some of the endothelial lining is destroyed, granulations develop and eventually, are transformed into fibrous tissue, adjacent surfaces may be bound together by firm adhesions in which lymph and blood vessels may develop Occasionally, especially if the inflammation is serofibrinous the process becomes chronic In relatively few cases, the effusion becomes purulent deep inflammation and granulomatous thickening of the serosa occur and this may undergo caseous degeneration Subsequent organization and fibrosis leave behind permanent thickening and adhesions of the membranes with distortions and retractions of adjacent structures The serous or purulent exudate may become loculated After some years if this is absorbed incompletely or very slowly the organizing walls of the pockets become infiltrated with calcium salts Calcification of the pleura is seen occasionally, calcification of the pericardium less often, calcification of the peritoneum very rarely

Tuberculosis of the Pleura—One or both pleurae may be affected The commonest form is fibrinous pleurisy and this usually overlies a pulmonary lesion Serofibrinous pleurisy develops in approximately 5 per cent of all cases of pulmonary tuberculosis it may also be a manifestation of generalized hematogenous tuberculosis This is probably the case if both pleurae or other serous membranes are involved simultaneously or in close succession Tuberculous empyema is uncommon except as a complication of pneumothorax natural or induced in which effusions are frequent the most serious forms are caused by ulceration and perforation of the pleura secondary to ulceration of an underlying pulmonary lesion Isolated fibrous adhesions may be left behind but after serofibrinous pleurisy heals, the pleura becomes widely or totally adherent almost always and if the inflammation was severe the resulting organization and thickening may cause retraction of the mediastinum diaphragm and chest wall The same is true to a more pronounced degree of healing tuberculous empyema

Fibrinous pleurisy may occur without lo

calizing symptoms but in a few cases is accompanied by the development of a severe sharp pain in the side immediately over the area of involvement or referred along the segmental distribution of the sensory nerves thus diaphragmatic pleurisy may cause pain in the trapezius ridge and in the upper hypochondrium The pain is usually aggravated by breathing and may last for a few hours to several days occasionally longer General symptoms of lassitude, possibly with low afternoon fever may last for a few days to several weeks

Serofibrinous pleurisy may develop as a complication of previously recognized pulmonary tuberculosis in which case the clinical onset may not be distinguishable from the exacerbation of a pulmonary lesion In other cases the presence of pulmonary tuberculosis may be unknown previously or the lungs may be found clear Small effusions may collect and disappear unknown to the patient The onset may be insidious with malaise and fever rising gradually to 101° or 102° F or it may be acute with a sudden sharp pain in the side chilliness malaise and fever rising quickly to 104° or 105° F The subsequent course may continue mildly or acutely The effusion may be small and become absorbed within a couple of weeks with complete subsidence of symptoms In the acute cases however high fever frequently continues daily for four to six weeks after which defervescence by lysis follows During this time the patient may lose 10 20 or more pounds in weight, become weak and have severe sweats Small effusions cause no local symptoms but large collections may produce dyspnea and cyanosis on account of the displacement of the heart, blood vessels and lung Convalescence usually starts after four to six weeks but occasionally is delayed for three to six months the fluid then becomes slowly absorbed leaving behind varying degrees of thickening and retraction

DIAGNOSIS —The diagnosis of dry or fibrinous pleurisy is made by detecting a friction rub or pleural crepitus but this may disappear soon or be entirely lacking The diagnosis of serofibrinous pleurisy is indicated by the physical and x ray signs of a basal ef[illegible] possibly with associated signs of [illegible]berculosis and of displacement of the heart. In the early stages thoracentesis yields clear straw-colored fluid which has the characteristics of an exudate and contains cells of a mononuclear occasionally polymorphonuclear type infrequently it is sanguinolent Tubercle bacilli usually are not discovered by microscopic examination because they are rather scarce. If possible 500 cc or more of fluid should be treated by centrifugation and the sediment inoculated on culture media and into a guinea pig the organisms are usually demonstrated in this way However, the failure to find tubercle bacilli even on inoculation does not necessarily exclude tuberculosis

TREATMENT —The treatment of fibrinous or serofibrinous pleurisy is determined by the severity of the process and of any associated lesions As a rule, localized fibrinous lesions do not require more than a few weeks of rest treatment The treatment of serofibrinous pleurisy is more important If the patient has pulmonary disease as well the pleurisy is regarded as a problem in the general treatment already described If no pulmonary lesions are demonstrated it must be remembered nevertheless that 20 to 30 per cent of these patients fall ill with pulmonary tuberculosis or some other form of the disease within five years Therefore the case should be treated as one of active tuberculosis with rest in bed for one to three months after the acute symptoms have subsided to be followed by another three to six months convalescence probably in a sanatorium. The indications for withdrawing the fluid from the pleural cavity are (1) at the start, for diagnosis (2) to relieve respiratory embarrassment from mechanical displacements (3) to dispose of any residual collection after the febrile symptoms have subsided and absorption seems to be too slow (4) to visualize the underlying lung if parenchymal lesions are suspected For the last mentioned purpo e 100 to 200 cc of air are [illegible] with a pneumothorax apparatus during evacuation of the fluid The [illegible] parenchyma may then show much more clearly in the roentgenogram. O[illegible] pneumothorax should be avoided since [illegible] interferes with healing and retards [illegible] of the pleural surfaces The prognosis of uncomplicated tuberculous pleurisy with effu ion is excellent if sufficient rest treatment

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of air through the tube into the pleura Effusion is kept down by aspiration to avoid drainage through the bronchopleural fistula into the lungs Since infection usually continues and healing of the bronchopleural fistula seldom occurs spontaneously thoracotomy for drainage is usually necessary and eventually extensive thoracoplasty The fatality rate is high because of the seriousness of the complication and frequently because of the extent of the underlying pulmonary tuberculosis

Tuberculosis of the peritoneum may be the result of hematogenous infection or of extension from local lesions such as retroperitoneal lymphadenitis or salpingitis Fibrinous inflammation in the visceral peritoneum at the site of intestinal ulcers is a common finding General involvement may be miliary, serofibrinous or plastic and adhesive Serofibrinous peritonitis may have an acute or insidious onset with constitutional symptoms like those described for serofibrinous pleurisy Abdominal pain and tenderness are usually slight or moderate occasionally very intense Constipation is a common symptom Diarrhea usually is an indication of intestinal ulcerations but the combination of these with generalized peritonitis is not common Abdominal distention may be great due to ascites and tympanites but in other cases the wall is spastic and scaphoid Signs of fluid may be difficult to demonstrate if the accumulation is small As adhesions develop the exudate may become loculated in pockets and the omentum and intestine matted

Exudative peritonitis is most common in children and young adults but may occur even in old people it is observed more often in Negroes than in whites and in females than in males Occasionally it is a complication of cirrhosis of the liver Except when it is such a complication or a part of generalized tuberculosis the prognosis for healing is good provided general rest treatment is instituted early and carried out long enough Mechanical symptoms may require evacuation of the fluid some prefer to do this by a small surgical incision Laparotomy is unnecessary in most cases Formerly, exposure of the diseased peritoneum to the air was supposed to be beneficial but this is doubtful In female patients tuberculosis of the fallopian tube may prolong the peritonitis and favor chronicity in such cases salpingectomy may be indicated After the disease becomes quiescent carefully graded heliotherapy may have a beneficial tonic effect

Plastic adhesive peritonitis usually is a later development of fibrinous or serofibrinous inflammation The serous surface becomes involved in a chronic granulating and organizing process which results in more or less extensive adhesions and thickening Fibrous contraction may produce narrowing of the lumen of the bowel the coils of which may be bound together in large inseparable tangles Between the hyperplastic and caseous lesions tuberculous exudate sometimes purulent, may be pocketed Abdominal examination may reveal irregular masses of involved omentum matted intestine caseous deposits or enlarged lymph nodes These may be numerous or confined to a single section such as the right lower quadrant surrounding the cecum Aside from the manifestations of chronic toxemia local symptoms may become distressing on account of the fixation and stenosis of the bowel There may be constipation obstipation or occasionally obstruction Rarely the intestine is perforated and tuberculous pus may drain from the peritoneum into it Treatment is general and symptomatic unless the disease is localized and accessible such as a hyperplastic process in and surrounding the cecum this may be resected surgically Postoperative abdominal fistulas which may be fecal are not uncommon

Tuberculosis of the pericardium may represent an extension from the pleura in which case the lesions are usually of a localized fibrinous hyperplastic or adhesive character giving rise to few or no symptoms Serofibrinous pericarditis is observed most often in association with acute or subacute lymphohematogenous dissemination of the infection Aside from the manifestations of toxemia symptoms and signs referable to tamponade of the heart may be found the embarrassment may be relieved by paracentesis Because the infection often is systemic the prognosis for recovery usually is poor The effusion may continue reaccumulating and after three to six weeks loculation may occur because of the formation of

is given Because of the hazard of pulmonary tuberculosis developing later, x ray examination of the chest every six to twelve months is advisable for any patient who has had tuberculous pleurisy

TUBERCULOUS EMPYEMA is related usually to some peculiar situation such as pleural ulceration and rupture or artificial pneumothorax and is considered in this connection Serous effusions develop in artificial pneumothorax in more than 90 per cent of the cases where the treatment is continued for months These may be absorbed rapidly, causing few or no symptoms In other cases the effusion becomes chronic and may undergo other changes A rich admixture of fibrin may collect in flakes threads or balls and the content of mononuclear cells may increase to 5000 or more per cubic millimeter In other cases there is a large output of polymorphonuclear leukocytes which rapidly undergo degeneration giving the effusion at first a cloudy appearance and later a thick light yellow or greenish creamy consistency Tubercle bacilli may be demonstrable easily microscopically and may appear in large clumps A thick coating of fibrin is deposited on all the pleural surfaces later to be transformed into granulation and fibrous tissue Unless the exudate is absorbed early organizing pleurisy enveloping the collapsed lung may bind this down and prevent its reexpansion Occasionally the empyema becomes thin and serous and is absorbed but more often chronic inflammation continues and generalized amyloidosis may result Thoracotomy for drainage is contraindicated because of the danger of introducing secondary infection and creating a permanent sinus of the thoracic wall Unless the lung reexpands readily while the fluid is removed by thoracentesis or by absorption extensive thoracoplasty is required to obliterate the pleural space approximating the surfaces so as to allow adhesion and healing

PNEUMOTHORAX in tuberculous cases is related either to the ulceration of a subpleural caseous focus or to the rupture of a subpleural bulla which has developed secondary to the fibrosis In the latter event the lung collapses but as a rule the pleura does not become infected nor is there any effusion The tear heals readily and the lung expands within several months In the former event however tubercle bacilli are invariably discharged into the pleura through the fistula, acute serofibrinous pleurisy develops and often goes on rapidly to tuberculous empyema Secondary infection with streptococci staphylococci or pneumococci is common creating a mixed infection empyema After the lung collapses the fistula may operate as a valve mechanism permitting the accumulation of air under great tension in the pleural space The fistula is usually chronic and seldom heals except after operative intervention Consequently the pleura is continually reinfected Sometimes too the pleural effusion or empyema escapes through the fistula into the lung on the same or opposite side causing acute tuberculous bronchopneumonia

The symptoms of pneumothorax may develop in a known tuberculous patient or in one who appeared healthy previously As a rule a sudden sharp tearing pain in the chest is experienced followed quickly by increasing shortness of breath and cyanosis The patient seldom loses consciousness but occasionally this accident may be the cause of sudden death In other cases the event is symptomatically silent particularly if the pleural perforation is tiny and the lung is partially anchored by adhesions which prevent its complete collapse in the latter case the pneumothorax is detected as a localized pocket If there is no infection the symptoms may soon subside with or without thoracentesis for the withdrawal of air and the patient experiences no difficulty while the lung reexpands With infection the symptoms of serofibrinous pleurisy develop acutely and examination reveals hydropneumothorax with varying degrees of displacement of the yielding mediastinum diaphragm and chest wall Thoracentesis at the start reveals a clear or cloudy effusion in which tubercle bacilli may be found alone or in combination with pyogenic organisms

Treatment is designed at first to relieve the acute mechanical displacement which is done by aspirating gas from the pleura at required intervals or it may be withdrawn continuously through an indwelling needle connected with an aspirating apparatus or to a rubber tube the other end of which is placed in a pan or bottle of water beneath the bed This mechanism prevents reflux

these is in proportion to the amount of caseous degeneration which occurred previously

Cervical lymphadenitis is a common form but in the United States has become much less prevalent since the early nineteen hundreds The disease which was known in earlier times as scrofula or king s evil has been reduced through the elimination of tubercle bacilli from milk and the prevention of massive infection in childhood The lesions may be confined to one or several nodes or may encircle the neck anteriorly from ear to ear The upper deep cervical nodes are most frequently affected as a rule the lesions are more pronounced on one side Infrequently the acute swelling is so marked as to impede the motion of the neck and to displace the trachea If the onset is insidious the lumps may be discovered purely accidentally Tenderness is slight or moderate unless the overlying tissues become involved The skin usually appears healthy but may become red tender and gradually thinned out until perforation occurs A thick or nummular purulent discharge follows and drainage may continue for a long time Neglect of the condition may result in fistulas in various parts of the neck and in the upper thorax Rest treatment if instituted early usually leads to healing of the lymphadenitis The swelling may disappear entirely or small nodes may persist with calcareous centers demonstrable by x ray Surgical treatment may be indicated when there is extensive abscess formation or if the involved nodes become so numerous and large that healing cannot be expected under simpler treatment Heliotherapy after the acute stage has passed may aid in the healing of fistulous tracts and general heliotherapy is thought by some to be helpful in chronic cases X ray therapy is considered by many to have a place especially after fistulae and scrofuloderma have developed However this treatment probably when too intensive has been known to accelerate the necrosis of inflamed and caseous nodes

Abdominal lymphadenitis may be part of a generalized infection or result from lesions in the intestine peritoneum or other adjacent organs Usually there are no specifically localizing symptoms but when the involvement is moderate or extensive vague abdominal pain constipation and indigestion may be complaints Sometimes the condition simulates chronic appendicitis Advanced wasting disease in infants and young children is known as *tabes mesenterica* Unless the lesions originally were extensive or part of generalized tuberculosis the tendency to heal is striking

Tuberculosis of the Urinary Tract.— The kidney is the most frequent site, the infection usually being hematogenous In the males the infection sometimes extends to the urinary tract from the genitals The disease is much more prevalent in adults than in children and is observed two to four times as frequently in males as in females The finding of microscopic tubercles in the kidneys is common at autopsy but gross lesions are detected in 10 per cent or less of all cases of chronic pulmonary tuberculosis The disease often occurs in patients who have never suffered from pulmonary disease the presumption being that the infection was carried from a lymphatic focus usually mediastinal Renal lesions may be latent for a long time before causing clinical symptoms The early lesion is usually in or near the glomeruli and bacilli may pass from this through the tubules to the papilla Caseation and ulceration may be limited or extensive resulting in the formation of small fistulas and the discharge of bacilli into the renal pelvis and ureter These more resistant structures also may be invaded then Often the kidney becomes more or less excavated Occasionally the caseous lesions may be encapsulated or the ureters become sealed off then calcareous changes may develop The bladder may be infected with bacilli carried in the urine tubercles and ulcers about the ureteral orifice appear and if the invasion is wide later fibrous shrinkage may reduce the capacity greatly Calcification of the bladder is rare Destructive renal tuberculosis at first is usually unilateral Bilateral disease may result from hematogenous or lymphogenous infection and possibly from reflux of urine from the tuberculous bladder

The symptoms include polyuria hematuria pyuria dysuria and strangury but at the inception renal tuberculosis usually is symptomless Similarly physical examina

fibrinous adhesions Caseation is observed occasionally, especially in Negroes and this may extend into the myocardium In the few cases of recovery the layers of the peri cardium may adhere completely and in time the shrinkage may lead to chronic constrictive pericarditis with functional impairment In this disabling situation the operation of cardiolysis may effect partial or complete relief in 60 per cent of the cases (Heuer and Stewart) Occasionally the pericardium be comes calcified

Tuberculosis of the Lymph Nodes — Lymph nodes may be infected by tubercle bacilli entering the lymphatic stream from a lesion in the tributary region or arriving by way of the blood stream Most often the lesions are limited to a single chain frequently the mediastinal system However, in generalized hematogenous forms of tuberculosis multiple scattered lymphadenopathies are demonstrated commonly in the superficial and deep chains The lesions may appear as acute subacute or insidious inflammatory swelling of the nodes with grad ual caseation and necrosis Periadenitis and agglutination with adjacent nodes may fol low, later liquefaction rupture and slough ing of the contents through the overlying tissues, particularly in the case of superficial involvement As the inflammation subsides, calcification of the caseous residues may de velop slowly during a period of years and the lesions may remain as permanently en larged firm usually discrete nodes Some times chronic fistulas usually superficial persist and these may burrow widely causing extensive degeneration of the skin and sub cutaneous tissues (scrofuloderma) More often lymphadenitis is of a mild hyperplastic type with only a minimum of caseation The lesions may be chronic or they may subside and become reactivated repeatedly after long or short intervals of time without any evi dence of liquefaction or sloughing Chronic caseous lymphadenitis particularly in the mediastinum is a potential source of danger even after long periods of latency Despite partial calcification these lesions may be the source of disseminations in childhood in adolescence and sometimes even in late adult life I have seen fatal tuberculous pneumonia in a woman of seventy caused by the rupture into the bronchus of a caseous node In the chronic systemic forms of tuberculosis the lymphatic system may harbor most of the lesions and account for the protracted ill health including exacer bations of low fever from time to time

Mediastinal and bronchopulmonary lymphadenitis is observed most often in young children following the primary infection Constitutional symptoms may be mild or entirely lacking Massive lesions may pro duce pressure giving a variety of symptoms such as stridulous cough simulating whooping cough constant or intermittent wheezing respiration sometimes simulating asthma less commonly stridor, dyspnea and cyan osis Localized pressures on the bronchi may irritate and compress the tube resulting in collapse of the lobe or of the lung or the development of nonspecific suppurative bronchopneumonia and possibly bronchiec tasis Perforation of the nodes through the trachea more often the bronchi may occur soon or after a lapse of many years dis charged tubercle bacilli may then be aspir ated into the lung causing tuberculous bron chopneumonia Calcified nodes similarly may ulcerate through the bronchi (bron cholithiasis) Physical examination usually is not helpful unless the mass is very large then it may be suspected by dulness and altered breath and voice sounds extending beyond the spine or sternum on one or both sides The roentgenogram reveals the lesions unless they are small and concealed by other structures the shadows include bulbous en largements of the hilum widening of the mediastinal density and the round and oblong homogeneous or granular opacities of calcification With few exceptions the tuberculin test is positive and often there are typical lesions also in the lungs or elsewhere Occasionally physical signs and symptoms of bronchial stenosis or of tracheal and venous obturation may be elicited The treatment is the general hy gienic rest regimen together with pediatric supervision in the case of children X ray therapy has been tried but usually is ill ad vised because of the possibility of aggravat ing caseation The same may be said of tu berculin therapy Under rest treatment mas sive enlargements may gradually subside eventually leaving very little trace or pos sibly only calcified residues The extent of

may appear in the urine While rest treatment is indicated in these cases the lesions usually run a chronic course and the prognosis for ultimate healing is not good Therefore after the acute inflammation has subsided surgical resection should be considered especially if the demonstrable lesions are limited and unilateral Removal of an epididymis for instance may prevent further invasion of the seminal tract The results generally are good

Tuberculosis of the Meninges and Central Nervous System —Tuberculosis of the meninges and central nervous system figures conspicuously among children in whom the infection proves fatal Deaths at this age are ascribed most often to generalized miliary tuberculosis or tuberculous meningitis In adults meningitis is a relatively infrequent cause of death even among those who have suffered from chronic pulmonary disease Occasionally however it is a terminal event in various forms such as tuberculosis of the genito-urinary organs or bones While leptomeningitis is the commonest manifestation the dura may contain a few hematogenous tubercles or may become involved by extension from an adjacent bony focus such as vertebral caries Limited hematogenous lesions usually cortical may appear also in the cerebrum less often in the cerebellum or spinal cord These may be single or multiple and in rare cases may heal eventually with calcification Such tubercles may be of a chronic granulomatous character gradually increasing in size and producing the clinical manifestations of tumor- the symptoms then depend on the location of the lesion The meninges may become involved secondarily

It is seen therefore that tuberculous meningitis may originate from a tuberculoma previously established in the cortex pia or dura or may develop as part of an acutely disseminated infection from some more remote source Thus it is a common complication of generalized miliary tuberculosis The distribution of the tubercles the perifocal congestion and the fibrinous exudate are characteristically basilar The regions favored are those about the circle of Willis the interpeduncular space the fissures of Sylvius and the optic chiasm Tubercles may be located in and close to the walls of arteries The contiguous brain tissue is edematous or infiltrated for a short distance

The patient may present the clinical picture of generalized miliary tuberculosis for several weeks before meningeal symptoms develop In other cases obvious chronic tuberculous disease may have been present usually in the chest Not infrequently however the patient especially if he is a child previously may have appeared perfectly well For no apparent reason the child becomes listless and irritable The appetite fails and he loses weight If he is too young to describe the headache it may be eloquently indicated by feeling or fumbling his head with his hands and by the sharp so called hydrocephalic cry' or the unmistakable and sustained scream of pain Vomiting is common usually sudden and often projectile sometimes precipitated by a change of position in bed The fever may rise to 103° F or more in the afternoon At first the pulse may be quick but later it becomes slow in proportion to the fever The pupils initially are contracted later dilated As the terminal or paralytic phase follows that of irritation the restlessness night terrors and outcries may give way to stupor whimpering and muttering The patient may be disoriented and wander from his bed There may be clonic contractions of single groups of muscles and not infrequently general convulsions Photophobia is common and there may be strabismus and blepharoptosis Monoplegia or hemiplegia may be observed The initial constipation and urinary retention usually is followed by incontinence

Early in the disease the neck and the muscles of the back and extremities may be sore and stiff The Kernig s sign is usually positive and there may be general hyperreflexia ankle and patellar clonus and a positive Babinski sign Later the muscles may become flaccid and reflexes diminished As the coma deepens the patient may execute athetoid movements Finally he becomes completely motionless the temperature varies widely and irregularly and sweating may be profuse In this unconscious state his eyes half closed and jaw agape he wearily breathes away his final hours

The duration of the disease varies from three to six or eight weeks occasionally

tion at the start may be entirely negative Later, slight tenderness may be elicited on palpation of the kidney or in the upper lumbar region posteriorly Constitutional symptoms if any usually are slight The condition is to be suspected particularly in a patient with pulmonary tuberculosis in the presence of unexplained albuminuria hematuria or pyuria especially the last two even if the quantity of blood or pus is small *Dysuria or cystitis not explained otherwise,* should always be investigated Tubercle bacilli usually are demonstrated on staining the sediment *after centrifugation of from* 500 to 1000 cc of urine or by culture and animal inoculation of this sediment, care being taken to eliminate smegma bacilli Examination may show small or moderate amounts of albumin an abnormal number of erythrocytes and pus cells Pyelography cystoscopy and ureteral catheterization are employed to demonstrate the extent and location of the lesions Nephrectomy is the treatment of choice unless there is more than slight involvement of the opposite kidney If no disease is demonstrated in the opposite kidney this operation leads to recovery in 50 per cent or more of the cases Lesions of the bladder if not extensive show a striking *tendency to heal after the infected* kidney is removed However if the bladder is widely destroyed and symptoms are severe *relief* may be afforded, if at all only by *surgical implantation of the ureters into* the intestine or the skin of the abdomen

Tuberculosis of the Genital Tract — Genital tuberculosis was found in 12 7 per cent of 1143 autopsies on tuberculous subjects by Auerbach at the Seaview Hospital of these 14 4 per cent were in males and 10 4 in females The disease is almost always hematogenous and secondary to preexisting lesions elsewhere in the body *In forty one* cases in females Auerbach found the fallopian tubes involved in 97 5 per cent, the uterus in *58 5 per cent* and the ovaries in 31 7 per cent The cervix is seldom affected the vagina and labia rarely The most com*mon sequel* of salpingitis is localized or diffuse peritonitis Both tubes may be involved but the lesions are usually unilateral There may be few or no localizing symptoms if any, they appear as dull vague pains in the lower abdomen accentuated perhaps during menstruation The menses may be scanty irregular or absent There may be slight or moderate leukorrhea and rarely tubercle bacilli are found in the discharge Pelvic and sometimes abdominal examination may reveal an elongated round mass a few centimeters in diameter in the pelvis The lesions may heal spontaneously if they are not very extensive but if they are chronic surgical resection is favored sometimes to eliminate the focus and prevent extension to the peritoneum

Male genital tuberculosis usually is mani*fested first in the epididymis but pathologic* examinations suggest that the initial focus usually is in the prostate the epididymal lesion being a secondary extension In 105 cases examined at autopsy Auerbach found the prostate involved in 95 2 per cent the seminal vesicles in 61 9 per cent the epididymes in 48.5 per cent and the testes in 20 5 per cent Ljunggren found associated involvement of the kidneys in 50 per cent of sixty cases of tuberculous epididymitis As the lesions progress extension to the opposite epididymis is common The bladder also may be affected secondarily Progressive disease may be followed by the establishment of sinus tracts perforating the scrotum and *allowing the discharge of tuber*culous pus to the outside

The onset of *tuberculous epididymitis* may be insidious with the development of *a nodular or diffuse infiltration* and this may subside and remain latent for a time More commonly the onset is acute with rapid swelling of the epididymis possibly with a serous effusion in the scrotum Later the testis may become swollen painful and even undergo softening Usually the acute inflammation subsides after several weeks leaving behind chronic lesions which may *slowly progress Examination* then may reveal a thickened more or less nodular epididymis and if the testicle participates this may be enlarged to twice or more its natural size The vas may be found thickened and nodular and rectal examination may reveal diffuse or nodular enlargement of the seminal vesicles and prostate *If any* of the lesions have liquefied limited fluctuant areas may be palpable If fistulas *develop tubercle bacilli may* be demonstrated in the discharging pus later they

may appear in the urine. While rest treatment is indicated in these cases, the lesions usually run a chronic course and the prognosis for ultimate healing is not good. Therefore after the acute inflammation has subsided, surgical resection should be considered, especially if the demonstrable lesions are limited and unilateral. Removal of an epididymis, for instance, may prevent further invasion of the seminal tract. The results generally are good.

Tuberculosis of the Meninges and Central Nervous System.—Tuberculosis of the meninges and central nervous system figures conspicuously among children in whom the infection proves fatal. Death at this age is ascribed most often to generalized miliary tuberculosis or tuberculous meningitis. In adults meningitis is a relatively infrequent cause of death even among those who have suffered from chronic pulmonary disease. Occasionally, however, it is a terminal event in various forms such as tuberculosis of the genito-urinary organs or bones. While leptomeningitis is the commonest manifestation, the dura may contain a few hematogenous tubercles or may become involved by extension from an adjacent bony focus, such as vertebral caries. Limited hematogenous lesions, usually cortical, may appear also in the cerebrum, less often in the cerebellum or spinal cord. These may be single or multiple and in rare cases may heal eventually with calcification. Such tubercles may be of a tumor-like granulomatous character, gradually increasing in size and producing the clinical manifestations of tumor, the symptoms then depend on the location of the lesion. The meninges may become involved secondarily.

It is seen, therefore, that tuberculous meningitis may originate from a tuberculoma previously established in the cortex, pia or dura, or may develop as part of an acutely disseminated infection from some more remote source. Thus it is a common complication of generalized miliary tuberculosis. The distribution of the tubercles, the perifocal congestion and the fibrinous exudate are characteristically basilar. The regions favored are those about the circle of Willis, the interpeduncular space, the fissures of Sylvius and the optic chiasm. Tubercles may be located in and close to the walls of arteries. The contiguous brain tissue is edematous or infiltrated for a short distance.

The patient may present the clinical picture of generalized miliary tuberculosis for several weeks before meningeal symptoms develop. In other cases obvious chronic tuberculous disease may have been present, usually in the chest. Not infrequently, however, the patient, especially if he is a child, previously may have appeared perfectly well. For no apparent reason the child becomes listless and irritable. The appetite fails and he loses weight. If he is too young to describe the headache, it may be eloquently indicated by feeling or fumbling his head with his hands and by the sharp so-called "hydrocephalic cry" or the unmistakable and sustained scream of pain. Vomiting is common, usually sudden, and often projectile, sometimes precipitated by a change of position in bed. The fever may rise to 103° F or more in the afternoon. At first the pulse may be quick but later it becomes slow in proportion to the fever. The pupils usually are contracted, later dilated. As the terminal or paralytic phase follows that of irritation, the restlessness, night terrors and outcries may give way to stupor, whimpering and muttering. The patient may be disoriented and wander from his bed. There may be clonic contractions of single groups of muscles and not infrequently general convulsions. Photophobia is common, and there may be strabismus and blepharoptosis. Monoplegia or hemiplegia may be observed. The initial constipation and urinary retention usually is followed by incontinence.

Early in the disease the neck and the muscles of the back and extremities may be sore and stiff. The Kernig's sign is usually positive and there may be general hyperreflexia, ankle and patellar clonus and a positive Babinski sign. Later the muscles may become flaccid and reflexes diminished. As the coma deepens the patient may execute athetoid movements. Finally he becomes completely motionless, the temperature varies widely and irregularly and sweating may be profuse. In this unconscious state, his eyes half closed and jaw agape, he wearily breathes away his final hours.

The duration of the disease varies from three to six or eight weeks, occasionally

deaths in the cases of children have been reported to occur in less than a week after the clinical onset Recovery is very rare

Lumbar puncture yields fluid which is usually clear and under increased pressure occasionally it is slightly turbid As the fluid stands in the tube a thin coagulum develops and tubercle bacilli may be found in this or in the sediment collected after centrifugation Otherwise guinea pig inoculation usually proves positive The number of cells in the fluid usually is 25 or more per cubic millimeter lymphocytes predominating The content of protein is found moderately or markedly increased glucose is decreased

Tuberculosis of Special Structures—The *breast* may be infected hematogenously but more often by extension from an adjacent lesion such as caries of a rib or tuberculous costal chondritis The breast may be diffusely swollen and tender but more commonly localized irregular nodular swellings increasing in size appear in one or more of the segments The conglomerate tubercles usually become caseous leading to the formation of abscesses from which cutaneous fistulas may originate The infection may burrow widely under the pectoral tissues If not too extensive incision of the abscess followed by cauterization with phenol may lead to healing If the glandular tissue is extensively involved mastectomy may be indicated

Tuberculosis of the myocardium while rare may occur through infection extending into it from the epicardium less often from the mediastinal lymph nodes or from the blood stream The lesions may be numerous and isolated or diffuse and caseous Alphonse described tuberculous phlebitis of the myocardial veins An extremely rare lesion is tuberculous endocarditis with valvular vegetations

Tuberculous arteritis of peripheral arteries is also rare sometimes due to the lodgment of infected emboli

Tuberculosis of the hypophysis is very rare Kirschbaum and Levy studied the chronic granulomatous type which may produce the symptoms of diabetes insipidus or of pituitary cachexia (Simmonds disease)

Tuberculosis of the thyroid and of the pancreas is rare and is observed only in generalized hematogenous infection or as an extension from an adjacent lesion Chronic thyroiditis and less often chronic pancreatitis on a tuberculous basis are occasionally reported

Tuberculosis of the adrenals if extensive produces the addisonian syndrome which may be rapidly progressive and fatal In these cases the adrenals are usually found to be caseous A few tubercles may be discovered here in generalized miliary tuberculosis and rarely, old calcifications

Tuberculosis of the Liver—Isolated gray hematogenous tubercles in the capsule or substance of the liver are not uncommon findings at the autopsy of patients who have died of pulmonary tuberculosis and they may be demonstrated in those who have never suffered from this disease In subacute and chronic forms of hematogenous tuberculosis particularly in young children and in Negroes numerous caseous tubercles of various sizes may be found in the liver but chronic destructive tuberculosis of the organ is very uncommon in these cases extensive caseous abscesses may be found Infection of the gallbladder or duct is also infrequent it is usually due to extension from an adjacent focus which may be in the lymph nodes

At Seaview Hospital Stemmerman found *tuberculosis of the bile ducts* in 3 per cent of 1500 autopsies on tuberculous subjects, usually the lesions were miliary or consisted of abscesses 1 to 20 mm in diameter

Tuberculosis of the spleen is a frequent sequel of hematogenous infection A few or many miliary tubercles may be found in the capsule or in the parenchyma or the organ may be enlarged and infiltrated with large caseous conglomerates the latter however is uncommon Encapsulation of caseous tubercles may occur and then these may persist as round nodular calcifications in the living they sometimes may be demonstrated roentgenographically

Tuberculosis of the ear may result occasionally from hematogenous infection but usually is a complication of cavitary pulmonary disease The middle ear may be infected through the eustachian tube usually one ear is involved but both may participate The process is subacute or chronic leading to abscess formation and slow per

foration of the drum after which a chronic fistula often persists Secondary infection then may occur The mastoid may become involved but this is uncommon at least in serious degrees The diagnosis is suggested by gradually increasing painless deafness tinnitus and a feeling of fulness in the ear of a patient with cavitary pulmonary tuberculosis Perforation of the drum is usually painless also Tubercle bacilli to be distinguished from nonpathogenic acid fast organisms said to live in the cerumen may be demonstrated in the discharging pus The inflammation occasionally heals without perforation of the drum leaving permanent partial deafness

The *nose* may become involved in lupus vulgaris the lesions of which may extend to the mucosa Picking of the nose by a tuberculous patient is supposed sometimes to cause infection of the mucosa and development of a chronic perforating septal ulcer *Tuberculosis of the paranasal* sinuses is observed rarely

Tuberculosis of the Larynx, Trachea, and Bronchi—Tuberculous laryngitis is one of the common complications of chronic pulmonary tuberculosis The lesions may be chronic and localized or acute exudative and diffuse The lesion usually appears first at the level of the vocal cords or the arytenoids in the posterior part of larynx There may be a diffuse swelling or tubercle formation in the interarytenoid space at the posterior end of one or both vocal cords or in the region of one or both arytenoid cartilages The inflammation may become almost completely resolved or it may progress with caseation and ulceration The irregular ragged shallow ulcers are found usually in the locations mentioned Later granulations may develop which have a serrated granular or tubercular form If extensive fibrosis may cause slight stenosis of the larynx The early symptoms are huskiness and hoarseness of the voice dryness and very slight soreness of the larynx This may be noticed only on awaking or after talking but usually continues beyond the time expected for simple catarrhal laryngitis Laryngoscopic examination then may show the redness and swelling or tubercle formation in the posterior part of the larynx Later if the lesions progress hoarseness becomes chronic and continuous and the dryness and irritation may cause moderate or severe coughing Pain is not usually a pronounced symptom unless deep invasion of the laryngeal cartilages occurs One of these the epiglottis may become greatly enlarged swollen red and finally deeply ulcerated Such extensive disease results in dysphonia severe dysphagia and salivation and the patient s nutrition may be seriously impaired because of his inability to swallow In treatment the most important principle is vocal rest, the patient being instructed to abstain from using the vocal cords He speaks in a labial whisper or resorts to written communication This together with proper treatment of the pulmonary tuberculosis usually results in healing during the early stages Later treatment with a specially constructed actual cautery may be necessary and very helpful Severe symptoms may be alleviated by the use of anesthetic sprays topically, or alcohol injection of the superior laryngeal nerve In any case of tuberculosis of the larynx the lungs should be examined since they are almost invariably involved

The bronchi leading from a tuberculous pulmonary cavity usually are invaded and in some cases lesions in the larger bronchi or trachea assume important clinical significance Shallow lenticular ulcers of the mucosa are not uncommon and more pronounced lesions develop occasionally in patients especially women with long-standing pulmonary disease The bronchial wall may be attacked also by lesions in contiguous lymph nodes The bronchial lesions consist of ulcers which are superficial or penetrate to or through the cartilage or of granulomatous and fibrous formations which may partially occlude the lumen Healing in the early stages leaves little or no scar but more advanced lesions may be followed by extensive organization of the bronchial and peribronchial tissues with contraction and cicatricial stenosis Occasionally a bronchus is completely occluded The affected bronchus may fail in its function as a drainage tube and in this event the related segment of the lung becomes involved with secondary pyogenic infection resulting in bronchopneumonia which may be suppurative and associated with bronchiectasis The diagnosis depends on eliciting the history of symptoms

of bronchial stenosis or ulceration such as persistent wheezing and the auscultation of rhonchi confined mostly to one side of the chest or to one lobe Similarly the symptoms and signs of associated suppurative pneumonia may lead to the diagnosis Roentgenographic evidence of obstructive emphysema or of diffuse pneumonia is suggestive Bronchoscopy discloses the ulcerous granulating or stenotic lesions which in some cases may be treated by topical applications Artificial pneumothorax to collapse the lung early may prevent the development of suppurative pneumonia and aid the healing of the bronchial lesion by stopping the flow of pus from a tuberculous cavity and by reducing motion of the bronchus Catheter drainage of occluded cavities thoracoplasty and pneumonectomy are now used with some success in the more serious cases

Tuberculosis of the Alimentary Tract —*Tuberculosis of the mouth* appears most often as ulceration of the tongue which becomes infected as a rule by extension from a laryngeal lesion or through an abrasion caused by biting or other trauma from the teeth The lesion is situated most often on the margin but may involve the dorsum especially at the base The ulcer at first is superficial but progressive infiltration and caseation often follow with extensive destruction of the muscle The chronic ulcers are often fissured and yellow caseous or red granulating tubercles may be found in their depths The indurated base is usually palpable The ulcer is usually single but others may appear The diagnosis depends on the finding of such a lesion in a tuberculous patient and may be confirmed by demonstrating the organisms in curettings from the ulcer Biopsy is to be avoided unless necessary Treatment consists of cauterization with the actual cautery, rarely the ulcer bearing area may be resected with success Local heliotherapy may be helpful

Tuberculosis of the lip is found usually under similar circumstances the lesion appearing much the same as that of the tongue An ulcer at the corner of the mouth may be fissure like and erode deeply

Tuberculosis of the salivary glands is rare possibly because of the alkaline reaction of the tissue (Vivoli *et al*) Sarnia reported a case of tuberculosis of the parotid gland which could not be distinguished clinically from malignancy mixed tumor or other types of inflammation

Tuberculosis of the pharynx is found most often in association with lesions of the tonsil Infection of the latter may be due to surface contamination or to hematogenous dissemination from a distant focus Upon examining 2000 pairs of tonsils removed surgically Long Seibert and Gonzales found that the incidence of tuberculous lesions depends roughly on the prevalence of tuberculosis in the community, it was 6.5 per cent in specimens from American Indians 2.5 and 0.25 per cent in those from Puerto Ricans and Philadelphians respectively The lesions are usually deep and focal In cases recognized clinically the tonsil is slightly or moderately enlarged and may show yellow or whitish caseous areas beneath the shiny mucosa later these break down leaving *ulcers of a grayish yellow ragged character* One or both tonsils may participate When the pharynx becomes infected secondarily the fauces soft palate and uvula become thickly seeded with granular miliary tubercles some of which have a minute yellowish center These coalesce break down and form fissured ulcers and the tissues may be slowly destroyed The pain is severe salivation profuse and dysphagia marked Such extensive disease is usually fatal Limited ulcers may appear on the posterior pharyngeal wall and these sometimes may be treated successfully with heliotherapy or direct cauterization Pharyngeal lesions may be associated with tuberculosis of the larynx

Tuberculosis of the esophagus is relatively rare The upper end may be involved by direct extension from severe tuberculosis of the larynx Tuberculous lymph nodes of the mediastinum after caseation may perforate the esophagus discharging their contents or the periadenitis may involve the esophagus without perforation In either event the cicatricial contraction may result in diverticula of the esophagus *Tuberculosis of the stomach* is reported in a few cases of pulmonary disease at autopsy (up to 2 per cent) The lesions usually extend to the stomach from a contiguous structure but they may be hematogenous or result from contamination by swallowed discharges from the lungs The gastric wall may be infiltrated

or there may be an ulcer, usually near the pylorus which grossly resembles carcinoma

The *intestine* is most frequently involved the commonest site being the lower ileum and cecum The mechanism of infection is principally from surface contamination with swallowed tubercle bacilli in patients with pulmonary tuberculosis (up to 70 per cent at autopsy) Much less often infection may be caused by primary invasion (*e g* contaminated milk) hematogenous dissemination or by extension from tuberculous peritonitis Infiltration of the intestinal mucosa and lymphoid tissue usually is followed soon by superficial ulceration the ulcers may extend rapidly or become localized and chronic with an organizing granulating base and overlying fibrinous or fibrous peritonitis Sometimes as in the cecum the proliferative granulomatous changes become very protracted leading to great thickening of the wall fibrous peritonitis and narrowing of the intestinal lumen the whole forming a tumorous mass Acutely progressive ulceration may involve several feet of the intestinal mucosa enclosing small islands of intact tissue Perforation of the wall by the ulcer is very infrequent Small ulcers may heal and the mucosa apparently regenerate

The initial symptoms are indefinite and considerable ulceration may be found in patients who have never had abdominal complaints At first there is slight to moderate loss of weight vague indigestion loss of appetite irritability and secondary anemia Local symptoms may appear early or late as a change in the usual rhythm of the stools A short attack of mild diarrhea may be followed by constipation and after an apparently normal interval this may recur After many weeks or months diarrhea may become frequent and finally the patient will have ten to twelve evacuations during the day and night the diarrhea being watery and foul seldom bloody The diarrheal attacks are associated often with colicky pains in the lower half of the abdomen aggravated perhaps by taking certain foods such as raw fruit The patient may become anemic and emaciated Physical examination usually reveals no palpable masses and frequently no tenderness although the patient may complain of a little soreness on deep palpation especially in the right lower quadrant In certain mild chronic cases the recurrent pain simulates simple chronic appendicitis, in fact, the appendix may be involved in the tuberculous process Sometimes this is not suspected until the lesions are discovered on routine histologic examination of the resected appendix In cases of tuberculous enterocolitis roentgenographic examination after a barium meal or enema may reveal spasticity filling defects and hypermotility of the lower ileum cecum and ascending colon Treatment consists first in proper general management and prescribed rest since these patients almost always have chronic pulmonary tuberculosis The most important adjuvant is regulation of the diet which should be bland raw fruits fruit juices and fat may have to be reduced or eliminated temporarily and vitamins given parenterally Medication to relieve pain and lessen the intestinal spasm may be indicated in the form of powdered opium or paregoric bismuth subnitrate or bismuth subgallate by mouth or calcium gluconate intravenously General heliotherapy in graduated doses may be of value after the acute symptoms have been controlled As a prophylactic against intestinal complications in patients with pulmonary disease McConkey has reported considerable success with the routine use of a cocktail of tomato juice and cod liver oil

Tuberculous ischiorectal abscess or *perianal abscess* and fistula is due usually to infection in a similar way and starts with a localized painful perianal swelling which becomes acutely tender within a few days or several weeks If not incised this may perforate the skin to the exterior less often the wall of the rectum with the discharge of nonodorous pus in which tubercle bacilli may be demonstrated The resulting fistula is apt to be chronic and later to require surgical treatment

J Burns Amberson Jr

PREVENTION OF TUBERCULOSIS

The observations that relative immunity may be conferred upon animals and that naturally acquired and limited tuberculous lesions have a similar effect in man have stimulated many attempts to develop means

of prophylactic vaccination and passive transference of immune bodies Killed devitalized and attenuated bacilli have been tried as vaccines administered by various routes as have fractions and products of the bacilli and of the lesions caused by them It has been shown that relative immunity may develop, usually in slight degree after the administration of living or dead virulent or attenuated organisms The duration of this may be a relatively few months, or some years Absolute protection against subsequent virulent infection has never been proved and no plan has justified itself thus far for universal application One of the better known vaccines, B C G an attenuated living strain of the bovine type of bacillus prepared by Calmette and Guerin, appears to have an immunizing capacity, and the degree of this is still under study Some believe that a return of virulence to such strains is not an impossibility

Measures which are assuredly effective for prevention include the following

Elimination of tuberculous animals and pasteurization of milk

Improvement of living conditions and education in personal hygiene

Adequate medical examinations to detect lesions in their incipiency usually in the preclinical phase

Sufficient and proper treatment of the early case to prevent excavation of the lesion and infection of 'contacts

Isolation of the infectious case

Rehabilitation of patients with arrested disease to prevent relapse

J Burns Amberson Jr

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FRIEDLANDER S BACILLUS INFECTIONS

The Organisms —Friedlander s bacillus (synonyms *Bacillus mucosus capsulatus B friedlanderi B pneumoniae Pneumobacillus Klebsiella pneumoniae Encapsulatus mucosus*) is an encapsulated short plump nonmotile gram negative rod with rounded end which grows to form mucoid gelatinous colonies on agar and a slimy surface pellicle in broth Three distinct serologic types A B and C are distinguishable by agglutination mouse protection precipitin tests and capsular swelling in specific immune serums and the two latter tests may be used for identifying the types directly from sputum exudates or cultures Other strains are classified as type X' although further specific types (D and E Cooper) have been noted Type B cross reacts in all tests with Type II pneumococcus especially with horse anti sera Type specificity resides in the capsular polysaccharide and this may be identified in cultures and in blood and urine of infected patients or animals While Friedlander s bacilli are readily distinguishable as a rule morphologically and culturally, biologic tests are unsatisfactory for absolutely differentiating them from closely related or

ganisms of the *rhinoscleroma* or *lactis aerogenes* groups so that they are often referred to as the Friedländer group of bacilli

Occurrence and Pathogenicity.—Friedlander s bacilli occur in the respiratory passages of from 2 to 25 per cent of normal persons in the normal intestinal tract even in infants and in the respiratory tract of mice guinea pigs and rabbits They have been found in soil dust, air and water They are pathogenic for man producing characteristic acute and chronic pulmonary infections and also suppurative infections in the upper respiratory passages in the intestinal biliary genital and urinary tracts and in serous cavities and meninges and give rise to septicemia and pyemia They produce septicemia and widespread lesions when injected into mice guinea pigs and rabbits

History —The organism was discovered by Friedlander in 1882 It was first described as a coccus and as the cause of pneumonia. This gave rise to considerable confusion and to a bitter controversy especially with Fraenkel The controversy was essentially resolved in 1886 by Weichselbaum who came around to the view now generally held namely that the pneumococcus is the chief etiologic agent of pneumonia and that Friedlander's bacillus may be the cause in a small percentage of cases

MAXWELL FINLAND

FRIEDLANDER S BACILLUS PNEUMONIA

Definition —Friedlander s bacillus pneumonia is a specific acute infectious disease caused by Friedländer's bacillus and characterized by massive mucoid inflammatory exudate of lobar or confluent lobular distribution in one or more lobes of the lung with a tendency to necrosis and abscess formation

Incidence and Distribution —Friedländer s pneumonia constitutes from 0 6 to 13 per cent of all cases of pneumonia in different series averaging 1 1 per cent in over 17 000 cases (Julianelle) It has been encountered in most parts of the world and in all seasons The disease is usually sporadic but contact cases and epidemics have occurred

Etiology —The etiologic relationship of the Friedlander s bacillus to pneumonia has now been authentically established in a large number of cases The organism has been found in pure culture during the first days of the disease in sputum lung and pleural fluids and in blood cultures, and has been obtained in direct smears and cultures from the blood and lungs at autopsy in rapidly fatal cases The pneumonias are caused predominantly by type A strains which are found in about two thirds of the cases Type B is next in frequency

Predisposing Factors —Pneumonia due to Friedlander s bacillus has its greatest incidence between the ages of forty and sixty years and is rarely encountered in infants and young children Chronic alcoholism malnutrition and general debility are encountered frequently in these cases Antecedent simple upper respiratory infections are relatively infrequent although occasional cases complicating influenza were encountered during the 1918 pandemic The disease may occur as a secondary infection following pneumonia due to other organisms particularly pneumococci or contrariwise it may be followed by infections with other organisms

Morbid Anatomy —The involved lung is heavy voluminous and noncrepitant with massive consolidation (lobar or confluent lobular) of one or more entire lobes Plaques of fibrin are found on the pleural surfaces The cut section of the affected areas usually has a smooth but mottled gray red or red brown surface from which thick stringy mucinous exudate often oozes as if under pressure The underlying lung often reveals soft areas in which alveoli appear liquefied and replaced by the mucinous exudate In older lesions there may be gray green purulent exudate with large areas of abscess formation Histologically the outsanding features are the necrosis of alveolar tissue the enormous numbers of encapsulated bacilli seen free or intracellular and the inflammatory exudate consisting of polynuclear large mononuclear (alveolar epithelial cells or monocytes) and red blood cells in varying proportions with only a small amount of fibrin

Symptoms and Course —In the majority of cases the onset is acute and begins like pneumococcus pneumonia with chill pleuritic pain cough and bloody sputum Profound prostration sets in early and delirium and distention are common Dyspnea and cyanosis also occur early and may be very

intense Free hemoptysis occurs in the majority of cases Sputum is usually copious but is often raised with difficulty because of its mucoid and sticky character, it may appear rusty but is more often brick red or bloody and gelatinous resembling currant jelly *Organisms are abundant in smears of* such sputum Vomiting and diarrhea are frequent and jaundice is present in many of the severe cases Occasionally there is hematemesis or melena Erythemas sometimes scarlatiniform occur and patients with bacteremia may have petechiae Herpes rarely occurs

Signs of consolidation may be made out early, but more often the classical signs are absent and there may be only dulness and muffled breath sounds even when massive density is visible in the roentgenogram This is presumably due to plugging of bronchi with viscid exudate Moist rales may be heard over some areas of the lung Involvement of the upper lobes or of multiple lobes is more frequent than in the pneumococcus pneumonias The fever is variable, it may be sustained or irregular, but usually ranges lower than in cases due to pneumococci

The disease may run a fulminating course ending fatally in twenty four to thirty six hours The average duration in Bullowa s cases was about five and a half days Death is usually associated with either peripheral vascular collapse pulmonary edema or extreme respiratory distress without pulmonary edema Recovery is sometimes by crisis but more often it is by lysis and then may frequently be followed by the chronic type of pulmonary infections to be described later

Laboratory Findings —The chief distinctive finding of interest is the large number of the characteristic bacilli seen in smears of the sputum Agar cultures made of the sputum directly yield the characteristic mucoid colonies usually in pure culture Blood cultures yield the same organisms in more than half of the cases and the organisms may be obtained almost regularly in pure culture by lung puncture or from pleural exudates even when the blood culture is sterile The bacilli may be typed directly from sputum exudate lung juice or blood culture growth by the capsular swelling with homologous rabbit antiserum as in the case of pneumococci The type-specific capsular polysaccharide may often be demonstrated in the patient s serum and in the urine during the acute disease, and it is also found in exudates Specific agglutinins may appear after the fifth day Total leukocyte counts below 6 000 occur in more than one third of the cases In other cases there is a moderate leukocytosis, with total counts reaching 25 000 or 30 000 in the presence of purulent complications

Roentgenograms usually show marked density developing early Areas of rarefaction may appear later, indicating abscess and cavity formation which in patients who survive long enough then shows evidence of healing and fibrosis

Diagnosis —Friedlander's bacillus pneumonia is suspected in any case of acute pneumonia with severe prostration occurring early, especially if there is bloody gelatinous sputum The diagnosis is based on demonstrating the characteristic encapsulated bacilli in smears and cultures of sputum as the only or predominant organism They may be typed directly by the Neufeld method The disease in some of its stages may simulate acute pneumonias due to other organisms particularly the pneumococcus pulmonary tuberculosis influenza ' pneumonia acute pulmonary infarction and bronchiectasis

Prognosis —The mortality in sporadic acute cases is high averaging about 80 per cent, regardless of whether or not bacteremia is demonstrated The mortality figures however are complicated because of the exclusion by some authors of some of the cases having a more chronic course in which the mortality is lower even when bacteremia occurs early

Treatment —The general and symptomatic treatment is the same as for severe cases of lobar pneumonia due to the pneumococcus There is some suggestive evidence of benefit from early and adequate treatment in type A cases with the homologous antiserum, but the results on the whole have been disappointing Sulfonamides have been widely used but the results are as yet difficult to assess Reports are available of recoveries with sulfapyridine sulfathiazole and sulfadiazine The latter appears to be the most promising of this group In view of the severity and rapid course it is advisable

to begin treatment with an initial intravenous dose of 0 1 Gm per kilogram of sodium sulfadiazine given as a 5 per cent solution in distilled water or as 0.5 or 1 0 per cent solution in physiologic saline Subsequent doses usually of 1 Gm each are given orally at 4 hour intervals and then adjusted so as to maintain high blood levels (about 15 mg per 100 cc), and adequate fluids (3 000 cc or more) given to permit an output of 1,500 cc or more per day Treatment in full doses for ten days or longer may be necessary

Complications —The commonest complication is delayed resolution with abscess formation and fibrosis of the lung (see below) Pleurisy is very frequent Empyema pericarditis meningitis nonsuppurative arthritis and superinfections with other organisms notably pneumococci and hemolytic streptococci have been noted Empyema and lung abscess which doesn t drain properly may require surgical intervention but this should be avoided in the latter instance if possible because a chronic sinusitis may result Section or crushing of the phrenic nerve may be resorted to in such cases

MAXWELL FINLAND

CHRONIC FRIEDLANDER S BACILLUS INFECTIONS OF THE LUNGS

Definition —Subacute or chronic infections of the lung caused by Friedländer s bacillus with a protracted and relatively benign course and expectoration of purulent nonputrid and sometimes bloody sputum Characteristically they are accompanied by abscess formation bronchiectasis and pulmonary fibrosis and exhibit a tendency to exacerbations of acute pneumonia

Occurrence, Etiology and Pathogenesis —The exact incidence of these chronic forms is difficult to establish but they are much less frequent than the acute Friedländer pneumonias Probably many cases go unrecognized and are included as tuberculosis or as other chronic pulmonary infections The relation of the Friedlander s bacillus to the disease is based upon finding the organism in large numbers and often in pure culture in sputum in abscess or pleural fluid or in blood cultures during acute phases Other organisms are also found in varying numbers in the latter stages

Morbid Anatomy.—Grossly the lungs present a picture of confluent bronchopneumonia with fibrosis bronchiectasis and abscess formation Since the upper lobes are usually involved, the gross picture resembles that of pulmonary tuberculosis with cavitation but there is no caseation The walls of the cavities consist of bundles of collagen fibers bearing connective tissue cells without the remains of alveolar walls Bronchi showing bronchiectatic changes often blend with foci of acute inflammation and with abscesses

Symptoms and Course —The disease usually begins as an acute Friedländer s pneumonia with slow lysis over a period of weeks, during which abscess formation and fibrosis of the lung occur In some cases there is a milder course from the start with low grade persistent fever cough with copious purulent sputum loss of weight and recurrent pleurisy The sputum is not foul (unless there is a mixed infection) and intermittently becomes blood streaked brick red or grossly bloody The disease may go on for several weeks and end in complete symptomatic recovery with apparent clearing of the lesions by x ray, or it may persist for many months or years In most instances there is chronic abscess formation and bronchiectasis with fibrosis which tend to reproduce the disease and give rise to relapses and frequent hemoptysis particularly after acute respiratory infections In more than three-fourths of the cases one or both upper lobes are involved so that the entire clinical and x ray picture closely resembles that of pulmonary tuberculosis with cavitation

Laboratory Findings —The typical encapsulated bacilli are always present in large numbers Secondary organisms including pneumococci staphylococci influenza bacilli and other common mouth inhabitants may also be abundant Bacteremia is less common in these cases but positive blood cultures have been obtained during the original acute pneumonia and during exacerbations Specific antibodies may be demonstrated early and persist for a few weeks Low grade leukocytosis is the rule except during acute phases when there may be a leukopenia X rays show thin walled cavities with or without fluid and later there

is fibrosis and retraction of the upper lobes, simulating tuberculosis

Diagnosis—In cases seen during the acute phase, the diagnosis is made when there is slow lysis and evidence of abscess formation with copious sputum The disease may be simulated by pulmonary tuberculosis with cavitation Many cases with the latter diagnosis in whom tubercle bacilli are not found are shown to have chronic Friedlander's infections The diagnosis depends on repeatedly demonstrating the characteristic encapsulated bacilli as the only or predominant organism in smears and cultures Staphylococcal pneumonias bronchomycoses lung abscess bronchiectasis and tumors of the lung must be considered in the differential diagnosis

Prognosis.—The mortality is said to be about 25 per cent Death may occur in the original attack after a slowly progressive illness of several weeks or months, or it may occur during an acute exacerbation of pneumonia with the same or other organisms, or as a result of complications such as pericarditis meningitis or following operation for empyema or lung abscesses Some patients apparently recover completely while most of the others continue to have signs and symptoms for as long as 20 years or more

Complications—Recurrent pleurisy is frequent Empyema usually encapsulated with thick mucoid pus may occur with or without relation to abscess formation in the lung Serous effusions are encountered which may be sterile or infected and may occur in patients who have purulent empyema elsewhere Recurrences of acute pneumonia and hemoptyses are the rule Axillary thrombophlebitis with acute arthritis has been encountered Pericarditis and meningitis may occur as terminal events

Treatment—On the whole the treatment is disappointing Cases are recorded in which the use of sulfonamide drugs during a relapse resulted in apparent clearing up of the infected focus but the results on the whole are unsatisfactory Empyema usually necessitates rib resection and this may also be necessary for large pulmonary abscesses which fail to drain Conservative treatment is recommended for abscesses in general in the hope that they will eventually drain into a bronchus

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FRIEDLANDER'S BACILLUS SEPSIS

Definition—Local or generalized infections caused by the Friedlander's bacillus frequently accompanied by bacteremia and associated with localized purulent infections in one or more organs

Septicemia with this organism is relatively uncommon and is less frequent than with the streptococcus, staphylococcus colon bacillus meningococcus or pneumococcus Several types are described (1) a pure septicemic type which has an acute and rapidly fatal course, (2) a pyemic type with multiple abscesses in many organs, (3) a septicemia with symptoms referable predominantly to one organ, and (4) one which is secondary to infection with other organisms

Portal of Entry—The organisms may gain access to the blood stream from any of the following foci the middle ear the lungs particularly where there is thrombophlebitis of the pulmonary vein, the intestinal tract which is common in infants, the liver especially when there is thrombophlebitis of the hepatic or portal vein the urinary tract the genital tract notably the prostate in males the adnexa or the puerperal uterus in females A large proportion of the cases are so called cryptogenic and the original focus cannot be determined even at autopsy

Etiology—Not all of the reported cases have sufficient information to identify the organism with certainty Little is known also concerning the type distribution in these cases The organism is recovered in pure culture from the blood and from foci of suppuration, and frequently from the urine

Occurrence and Predisposing Factors—Many of the cases occur in infants children and young adults of both sexes differing in these respects from the pneumonias Alcoholism cirrhosis of the liver and diabetes are particularly frequent in the adult cases

Morbid Anatomy—The dominant feature is the finding of metastatic abscesses in the liver lungs and kidneys Only those in the lungs are characteristic The pus in the abscesses is usually mucoid and tenacious and the characteristic organisms are readily found in large numbers in smears and are usually in pure culture Ulcerative endocarditis meningitis and involvement of serous cavities are sometimes encountered

Symptoms and Course —The onset may be abrupt with severe chills or it may be insidious with high continuous or intermittent fever and general malaise with or without chills Vomiting and diarrhea are common Rashes occur and may be either scarlatiniform maculopapular or petechial in character There is an acute fulminating type described (Blumer and Laird) with a hemorrhagic septicemia in which intestinal symptoms predominate and in which changes in the intestine similar to those of typhoid fever are found at autopsy In some cases particularly in adolescents the course may simulate typhoid fever in every respect including the leukopenia In others the picture is dominated by some local lesion such as abscesses of the kidney, lungs prostate or liver or by a cholecystitis with ascending infection or there may be perforation of the intestine with peritonitis In the cases with liver abscesses jaundice may be prominent The disease may be of short duration or last for several weeks Meningitis or endocarditis may occur terminally

Diagnosis —This depends on finding the Friedlander s bacillus in blood cultures or on demonstrating the organisms in characteristic pus from metastatic lesions

Prognosis —The mortality is high but except in cases with pyemia recoveries are recorded in all types of cases including some which have shown a persistent bacteremia for some time The prognosis is particularly favorable in cases in which there is a predominant focus such as the prostate which is accessible to surgical drainage

Treatment —Sulfonamide drugs particularly sulfadiazine are indicated in full doses and an effort should be made to maintain high blood concentrations (about 15 mg per cent) for two or more weeks Specific serotherapy may also be used as an adjunct Accessible foci should be drained surgically

Maxwell Finland

FOCAL INFECTIONS DUE TO FRIEDLANDER S BACILLUS

Occurrence —According to some writers notably Baehr *et al* these represent the bulk of infections with the Friedlander s bacillus and they assign only a secondary role to the pulmonary infections They consider the most common infections caused by the Friedlander's bacillus to be in the abdomen and to originate in the intestinal tract These include appendiceal and subphrenic abscesses and peritonitis In most of the cases the organisms are obtained in pure culture but in a large proportion they are found together with the colon bacillus An epidemic form of diarrhea in children has been ascribed to the Friedlander's bacillus The urinary tract is the next most frequent site of infection Here and in infections of the gallbladder and bile ducts associated defects particularly those causing obstruction are present in almost all cases in which suppuration occurs Positive cultures may be obtained from the duodenal bile in some of the cases of biliary tract infections Occasional cases have a course simulating catarrhal jaundice Prostatitis salpingitis infections of the skin and of the uterus and vagina have all been encountered Suppurative arthritis is usually a metastatic lesion and ulcerative endocarditis occurs in cases with associated bacteremia Meningitis may occur following sinusitis otitis media or following trauma

Course and Treatment —The course depends on the site of the lesion Transient bacteremia may occur in any of these cases In acute severe cases especially those with bacteremia intensive chemotherapy supplemented by specific serum should be used Surgical drainage is indicated whenever collections of pus become accessible Urinary tract infections are amenable to treatment with sulfathiazole or sulfadiazine Where obstructive lesions of the intestinal biliary or urinary tract are present the obstruction must be relieved if possible in order to bring about a cure of the infection

Maxwell Finland

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sinuses and in the discharge are found either the characteristic sulfur granule with its clubbed ends or small tangled masses of gram positive branching filaments which may or may not be partially acid fast

History —In 1877 Bollinger found the ray fungus in a disease of cattle known as "lumpy jaw" it was named *Actinomyces bovis* by Harz. J Israel, in 1878 discovered the disease in man and pointed out the identity of the two infections Lord in 1910 demonstrated that *Actinomyces* pathogenic for guinea-pigs could be found in the gums and tonsils of apparently normal individuals In 1914 Schottmüller isolated a streptothrix from the lesions of a patient with rat bite fever The work of Dawson in 1932 indicates that this type of rat bite fever is caused by the same organism that produces erythema arthriticum epidemicum (Haverhill fever) It is generally related to the *Actinomyces* and should be called *Actinomyces moniliformis* or *Actinomyces haverhilli*.

Etiology —Actinomycosis is widely disseminated and is the most common of the highly fatal mycoses The disease occurs most frequently in males

Bacteriology —The organism occurs in pus or tissues as lobulated or spherical granules which vary in size from very minute particles to forms about 1 mm in diameter Pure cultures are readily obtained from material aspirated from unopened abscesses but isolation is very difficult from draining sinuses because of the overgrowth from contaminating bacteria *Actinomyces bovis* is anaerobic and grows best at 37° C in glucose agar in a zone 5 to 10 mm below the surface

Actinomyces asteroides (*Streptothrix asteroides* atypical *Actinomyces Cladothrix* or *Nocardia*) is aerobic and grows on ordinary laboratory media at room and incubator temperatures The colonies are chromogenic and have the consistency of tubercle bacilli The granules are less compact than those of the true sulfur granule of *Actinomyces bovis* The filaments are gram positive frequently show branching and are more or less acid fast True club formation is absent but club shaped swelling of the terminal portion of the filaments may be observed Pure cultures of some strains produce a rapidly fatal disease in guinea pigs in ten to twenty days

Immunology —Not much is known about the serologic reactions of patients with actinomycosis

Pathology.—Actinomycosis may develop in any part of the body A granulomatous lesion is produced which is surrounded and intersected by new connective tissue Multiple interconnected abscesses form which, on rupturing to the surface produce multiple sinuses The local lesions spread by direct extension through the connective tissue rather than by way of the lymphatics although metastatic lesions appear in various parts of the body as a result of showers of infected emboli Colonies of the invading organisms are surrounded by mononuclear cells with an occasional giant cell and numerous polymorphonuclear leukocytes are found in the necrotic areas and in the walls of the sinuses

Symptoms —The clinical symptoms vary somewhat depending upon the part of the body involved

Cervicofacial actinomycosis accounts for more than 50 per cent of all instances of the disease Infection takes place through the mucous membranes of the gums mouth pharynx or larynx The whole infected area becomes indurated or wooden in consistency and this extends beyond the apparent area of inflammation The overlying skin has a dark red or purplish color and a lumpy uneven surface As the infection spreads to the surface multiple sinus tracts appear With internal extension the bones of the skull and even the meninges and brain may be involved Trismus develops when the muscles of mastication are involved and dyspnea when there is pressure on the larynx The lymph nodes of the neck usually are not involved Pain is not a prominent feature and the patient s general health is not much affected so long as the disease remains localized in the area of the face and neck

Thoracic actinomycosis occurs in about 15 per cent of the cases and produces cough sputum increasing dyspnea slight fever loss of weight and strength night sweats pallor and emaciation The sputum contains blood in about half the cases and sometimes a fatal hemoptysis occurs Pleural pain is common and effusions not infrequent After the disease has reached the pleura it usually involves the thoracic wall extends through the subcutaneous tissues and produces localized areas of induration with suppurating

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HAVERHILL FEVER

(*Erythema Arthriticum Epidemicum*)

Haverhill fever was first recognized as a clinical entity in this country in 1926 when Place Sutton and Willner reported an epidemic of 86 cases which occurred in Haverhill Massachusetts Eight years later Place and Sutton summarized the symptomatology of the disease as follows (1) An abrupt onset with chills fever malaise vomiting and headache (2) An early eruption, rubelliform or morbilliform occurring first and often only on the extremities especially about the ankles and wrists and tending to become hemorrhagic (3) A multiple arthritis of varying but often of severe and crippling degree (4) A fever with abrupt rise and remission in from two to five days, after a few days of relative freedom from symptoms a recurrence at which time the arthritic manifestations appear (5) A strong tendency to occur in epidemic form

Etiology —Haverhill fever is caused by an organism which was named by Parker and Hudson *Haverhillia multiformis* after studying cultures from twelve cases of the Haverhill epidemic It is recoverable from the joints of patients with the disease There is still confusion as to whether this organism should be classified as an actinomyces or as a member of the family *Bacteriaceae* More recently there has been a tendency to call the organism *Streptobacillus moniliformis* Serum from patients with Haverhill fever show agglutinins for the organism in high dilutions

Differential Diagnosis —Haverhill fever should be differentiated from rat bite fever whether due to *Spirillum minus* (Sodoku) or *Streptobacillus moniliformis* (bacteriologically indistinguishable from the etiologic agent of Haverhill fever) Rat bite fever, as so far reported always follows the bite of a rat or similar animal rarely produces any arthritis and has no tendency to occur in epidemic form While Haverhill fever has been known to follow the bite of a rat, it generally results from drinking contaminated milk

Haverhill fever must also be differentiated from rheumatoid arthritis erythema multiforme, influenza, and undulant fever

Prognosis —Only a few deaths have been reported The patients usually recover in from two weeks to two months

Treatment —Treatment is largely symptomatic Arsenicals such as neoarsphenamine have been tried with questionable success in a few cases

W J Stainsby

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THE MYCOSES

ACTINOMYCOSIS

Definition —Actinomycosis is a chronic granulomatous infection caused by several species of the genus *Actinomyces* The disease is characterized by the development of numerous abscesses which break down and develop multiple sinuses In the walls of the

BLASTOMYCOSIS

Definition.—Blastomycosis is a chronic granulomatous disease which may be confined either to the skin or lungs or disseminated throughout the body

History —The disease was first described by Gilchrist in 1894 and by Gilchrist and Stokes in 1896 It is found frequently throughout the western hemisphere but only sporadically in Europe and is usually called American blastomycosis or Gilchrist s disease and should not be confused with European "blastomycosis which is caused by *Cryptococcus hominis* (*Torula histolytica*)

Etiology—In previous editions it was stated that blastomycosis was most prevalent in the Chicago area Now it is known to be equally common in Louisiana Tennessee North Carolina and other parts of the country The disease is nine times as frequent in males as females

Bacteriology—The morphologic studies of Conant and the serologic investigations of Martin show that all strains of *Blastomyces dermatitidis* are morphologically and antigenically identical Sputum pus or biopsy material should be streaked heavily on Sabouraud s slants and on blood agar plates The slants are kept at room temperature but the blood agar plates should be incubated at 37° C The primary growth may be slow and cultures should be watched for two or three weeks On blood agar the colonies are small waxy and wrinkled and when emulsified in water and examined fresh under the microscope show typical budding double contoured yeast like forms (7–10 microns) identical in appearance with those found in the lesions

Immunology—Many patients develop a sensitivity to the products of *B dermatitidis* and give a skin test analogous to the tuberculin reaction Martin has found that patients with extensive involvement usually show a positive complement fixation when the whole yeast organism or certain of its extracts are used as the antigen The test is negative when the lesions are small or well localized and becomes negative in the systemic cases after recovery

Pathology—The primary skin lesions may be of a superficial verrucous type with little ulceration or gummatous like with open craters The multiple subcutaneous abscesses found in the systemic type of blastomycosis are analogous to cold abscesses in tuberculosis When the disease spreads from the skin bones or other organs to the lungs it produces the appearance in the x ray, and at necropsy, of a miliary hematogenous tuberculosis

Primary infection in the lungs often is localized to one or more lobes and may be *confused with atypical pneumonia tuberculosis* or lung abscess The microscopic picture simulates that of tuberculosis but there are usually many small microscopic abscesses with a polymorphonuclear reaction scattered throughout the lesions The characteristic budding organisms are found in the giant cells in the granulation tissue between the cells and about the edges of the necrotic areas

Symptoms—*Cutaneous blastomycosis* occurs most frequently on the face neck or extremities The primary lesion usually begins as a small reddish papule or papular pustule which slowly increases in size and is soon capped with a crust There is epithelial hyperplasia giving the lesion a verrucous appearance Minute epidermal abscesses appear about the edges of the lesions and some lesions break down to form deep crater like ulcers with hard raised edges The subjective symptoms are mild pain is minimal and the patches are not sensitive to pressure The regional lymph nodes usually are not enlarged and the general health of the patient is not impaired so long as the disease is confined to the skin

Systemic Blastomycosis—Patients with primary pulmonary blastomycosis have fever night sweats loss of weight cough sputum which is frequently bloody leukocytosis increased sedimentation rate and physical and x ray evidence of extensive pulmonary disease The lesion usually is incorrectly diagnosed as pulmonary tuberculosis but it may be mistaken for primary bronchogenic carcinoma Sinus formation is rare as long as the disease is confined to the lungs but in the systemic cases where there are multiple lesions of the bones and involvement of the internal organs it is frequent and characteristic

Diagnosis—Cutaneous blastomycosis is readily diagnosed by its characteristic lesions but the diagnosis should be confirmed by finding the organisms in the pus

foci and multiple sinus formation There may be extension to the mediastinum esophagus and pericardium

Abdominal actinomycosis is found in 20 to 30 per cent of the cases and represents a highly fatal form of the disease The earliest signs are usually in the ileocecal region and are associated with the development of an indistinct irregular mass which is not painful as a rule and shows no characteristic features This may be the first manifestation of the disease or it may be preceded or accompanied by fever, chills night sweats intestinal colic and vomiting As the disease progresses there is usually involvement of the liver and spleen and symptoms of cystitis and pyelonephritis may appear Jaundice may be present Involvement of the central nervous system may occur in the terminal stages

Actinomycotic mycetoma is occasionally encountered and usually is caused by *Actinomyces asteroides* (See *Maduromycosis*)

Diagnosis —The diagnosis is based on the clinical syndrome, the finding of the sulfur granule in the exudate or lesion or the cultivation of the organism Biopsies of the sinus tract should be made when direct examination of the exudate fails to show granules Frequent and repeated study of the exudate both in fresh preparations and with the Gram stain is imperative Cultures are reliable in the yeast like mycoses but not in actinomycosis The cervicofacial forms must be differentiated from glanders tularemia tuberculosis and osteomyelitis The pulmonary form simulates tuberculosis pulmonary abscess tularemia and other mycoses The abdominal form may be mistaken for chronic appendicitis amebiasis typhoid fever carcinoma of the intestines tuberculosis liver abscess psoas abscess and sarcoma of the retroperitoneal tissue or of the iliac bones

Prognosis —The prognosis is best in the localized skin and cervicofacial types and becomes progressively worse with the thoracic abdominal generalized and neurologic types

Treatment —The general resistance of the patient should be supported as in tuberculosis by rest in bed and good food supplemented by vitamins especially cod liver oil and fruit juices The cervicofacial form should be treated by surgical drainage potassium iodide by mouth local x ray therapy and by sulfonamides Potassium iodide should be administered by the method prescribed for blastomycosis Ethyl iodide which is volatile, has been used successfully in some instances of pulmonary actinomycosis It is administered with an inhaler of the type made by Warren Collins Instrument Company of Boston The dose is measured in cubic centimeters in a graduated centrifuge tube attached to the instrument, and should begin with 0 25 cc t i d and increase by 0 25 cc every three or four days until as much as 1 cc t i d is being employed Colebrook advises either autogenous or stock vaccines as a supplement to the iodide therapy, giving a dose which contains from 5 000 000 to 10 000 000 mycelial fragments at intervals of five days

Sulfanilamide sulfathiazole and sulfadiazine have been used with some success in actinomycosis The best medical therapy is the combination of potassium iodide by mouth with sulfathiazole or sulfadiazine This treatment offers the only hope for abdominal and generalized infections and should be continued for three to five months

David T Smith

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good prognosis when given the treatment described for blastomycosis

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COCCIDIOIDAL GRANULOMA

Definition—Coccidioidal granuloma is a chronic generalized granulomatous disease with a high mortality The *primary* infection is analogous to the primary stage of tuberculosis

History.—Posadas and Wernicke recognized the disease in Buenos Aires in 1892 Rixford reported a case from California in 1894 and Rixford and Gilchrist studied a series of cases in 1896 In 1900 Ophüls and Moffitt cultivated the organisms and demonstrated that it was a fungus and not a protozoan

Incidence—The disease is encountered most frequently in southern California but may be found anywhere in the Southwest and appears to be spreading eastward Thousands of soldiers in the Army camps in the Southwest have contracted the benign primary infection and a certain number of them will probably develop the severe granulomatous type of disease in future years The disease occurs at all ages from three months to seventy years but is most prevalent between the ages of twenty five and fifty five In one series of 211 cases 83 per cent were in males

Etiology—The causative agent is *Coccidioides immitis* Emmons has shown that the organism is present in rodents in the endemic area and Meyer and Stewart succeeded in isolating the organism from the soil by guinea pig inoculations The organism may be introduced into man through a scratch or abrasion of the skin although the more usual method is inhalation which produces an atypical type of bronchopneumonia

Bacteriology—*Coccidioides immitis* multiplies in the tissues by endosporulation The organism is a sporule with a thick hyaline capsule varies from 11 to 70 microns in diameter and contains from 10 to 200 endospores When infected tissues sputum or other discharges are planted on Sabouraud s medium the endospores germinate and grow out as mycelia Laboratory infections have occurred by accidental inhalation of the chlamydospores from cultures

Immunology—All strains of *C immitis* apparently contain identical antigens During the course of the primary infection the patient develops precipitins and complement fixing antibodies and the skin becomes sensitive to coccidioidin The precipitins and complement fixing antibodies slowly disappear after recovery but the skin sensitivity, like that to tuberculin is relatively permanent

Pathology—In chronic coccidioidal granuloma the organisms are surrounded by epithelial cells giant cells lymphocytes and plasma cells Abscess formation is more frequent than in tuberculosis especially in the bones and subcutaneous tissues Occasionally granulomatous masses reach a considerable size without suppuration and resemble fibrosarcoma or fibromyxosarcoma Abbott and Cutler described three types of meningeal lesions one is practically identical with tuberculous meningitis a second has larger more granulomatous lesions and the third shows a thick accumulation of plastic exudate

Symptoms—In some areas in the Southwest positive skin tests with coccidioidin have been found in 50 to 84 per cent of the population indicating that primary infection with *C immitis* is very common but usually asymptomatic When the reaction to infection is severe enough to be recognized as a disease the symptoms signs x ray changes and course of the disease parallel that of primary tuberculous infection The patients have malaise anorexia chills fever headache backache night sweats and pleurisy The cough produces a scant amount of mucoid or mucopurulent sputum which contains the characteristic spherules of *C immitis* The organisms have been found in pleural fluid Roentgenograms of the lungs may show thickening of the hilar region peribronchial thickening or patches of nodular or bronchial pneumonitis The larger more solid lesions may break down and leave thin walled cavities which usually heal in a few weeks or months but may persist for

expressed from the small abscesses in the edge of the lesion, by culture or by biopsy In the systemic form the organisms can usually be grown from the sputum or from pus aspirated from a subcutaneous lesion A positive complement fixation is diagnostic but a negative test does not eliminate the possibility of the disease

Prognosis —The prognosis is good in cutaneous blastomycosis, but very poor for the pulmonary and systemic forms of the disease Martin and Smith found that 92 per cent of the patients with the generalized form of the disease had died within two years The prognosis in the pulmonary form can be improved by early diagnosis and prompt and adequate treatment Several patients treated in the Duke Hospital Clinic *have remained well for periods as long as* five to eight years

Treatment —Potassium iodide is the standard drug used for the cutaneous pulmonic and systemic forms of the disease but patients who have become sensitized to the products of the fungus as demonstrated by the presence of a positive skin test may show rapid progression of the disease after the administration of this drug If the patient is sensitive to a stock or autogenous vaccine he should be desensitized by the injection of gradually increasing amounts of the vaccine at forty eight to seventy two hour intervals for ten to fifteen doses before potassium iodide is given Both the nonsensitive patient and the desensitized patient should receive an initial dose of 3 drops t i d of a saturated solution of potassium iodide after meals The dose should be increased by 3 drops each day up to 30 to 40 drops t i d As much as 300 to 400 drops have been given in a single day Sensitivity to iodides may develop and necessitate the discontinuance of the drug After a rest period of seven to ten days it should be tried again

Ethyl iodide inhalations may be used as a supplement or as a substitute for potassium iodide The dose and method of administration is described in the section on actinomycosis

Sodium iodide may be administered intravenously and as much as 4 Gm per day have been given without harmful effects

Local x ray therapy for cutaneous blastomycosis has been highly successful in the Duke Hospital Clinic when given simultaneously with potassium iodide and subsequent to desensitization of the sensitive patient Local application of maggots was used successfully in one case of blastomycosis where the disease was limited to an osteomyelitis of the elbow

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GEOTRICHOSIS

The bronchi and lungs and occasionally the mouth and intestinal tract may be attacked by one or more species of the genus *Geotrichum* The oral lesions resemble thrush and the pulmonary infection simulates blastomycosis Usually the patient has symptoms of bronchitis or of a rather mild but chronic type of bronchopneumonia In the more severe forms of the disease blood may be present in the sputum and cavities develop in the lungs The *Geotrichum* is frequently a secondary invader in chronic Friedlander's bacillus infection of the lungs and occasionally in tuberculosis

Bacteriology —The organism grows readily on Sabouraud s medium at room temperature and at 37° C There is a budding form of *Geotrichum* which is readily confused with the budding form of *Blastomyces* but this budding form is always accompanied by the rectangular conidia which are characteristic of the genus

Treatment —The oral lesions respond to the gentian violet treatment described for *Monilia albicans* The intestinal form should receive oral doses of gentian violet in salol coated capsules in doses of 32 mg t i d The bronchial and pulmonary forms have a

portal of entry is frequently in the area about the mouth there is ulceration of the intestinal tract and adenopathy severe enough to suggest Hodgkin s disease

The organism is found in the tissues as a large (10 to 30 microns) round doubly con toured form with multiple small buds about the periphery which were originally mis taken for endospores It grows readily on Sabouraud s medium and on blood agar Conant found that the method of growth and budding on blood agar was more like *Blastomyces dermatitidis* than *Coccidioides immitis*

The disease is usually fatal

The *treatment* suggested for coccidioidal granuloma should be given but supplemented by sulfonamides

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CRYPTOCOCCOSIS

(*Torulosis*)

Definition —Cryptococcosis is a subacute or chronic highly fatal infection which may involve any part of the body but which has a marked predilection for the brain and meninges

History —In 1894 Busse and Buschke isolated from a fatal case with multiple lesions of skin and viscera, a yeast like organism which they called *Saccharomyces* but which has now been definitely identified as *Cryptococcus hominis* (*Torula histolytica*) This disease is called "blastomycosis" in the European literature and "European blastomycosis" in America, to distinguish it from American blastomycosis, or Gilchrist s disease which is caused by *Blastomyces dermatitidis* In the series of cases reported in this country by Stoddard and Cutler in 1916 under the name *Torula* there was no involvement of the skin Freeman collected forty three cases in 1931 Levine analyzed sixty cases in 1937 and Reeves and Butt seventy-one cases in 1941

Etiology —Cryptococcosis occurs in all parts of this country and in scattered areas throughout the world Benham has found nonpathogenic strains and strains of low pathogenicity on human skin

Bacteriology —*C hominis* grows readily on Sabouraud s medium the initial colonies appearing after four to twelve days incubation at 37° C The colonies are medium in size soft mucoid with a creamy color On examination the oval or slightly elongated cells 5 to 6 microns in diameter are surrounded by large capsules which are outlined clearly in india ink preparations This fungus multiplies by budding it does not form ascospores or mycelium

Immunology —Patients usually develop neither precipitins agglutinins nor complement fixing antibodies but filtrates from cultures have given positive kin tests of the delayed type

Pathology —Mook and Moore have described acneiform pustules granuloma like ulcers deep-seated abscesses and nodules which may increase in size and simulate myxomatous tumors Giant cells and 'foam cells are numerous fibroblasts lymphocytes and plasma cells are present but there is a remarkable paucity of poly morphonuclear leukocytes In several in stances the tissue reaction was very similar to that seen in Hodgkin s disease The central nervous system lesions may resemble tuberculous meningitis or there may be a diffuse granulomatous meningitis with the development of cyst like structures in the cortex The encapsulated organisms are present both in and outside of giant cells but there is an almost complete absence of leukocytes

Symptoms —The patient may present single isolated abscesses subcutaneous tumor like masses or multiple subcutaneous abscesses as in the original case of Busse and Buschke The primary pulmonary lesions resemble the more acute forms of re-infection tuberculosis but the lungs may present the picture of miliary tuberculosis in the generalized form of the disease

In the more common cerebral type of infection the onset is insidious with head ache dizziness vertigo and stiffness of the neck Occasionally the onset is sudden with violent and excruciating headache and

years Sensitivity to coccidioidin appears after seven to fourteen days and skin lesions resembling erythema nodosum or erythema multiforme develop in 2 to 5 per cent be tween the fifth and fourteenth day of the disease and persist for one to four weeks This form of the disease has been known for years as Valley fever Desert fever San Joaquin fever or as the bumps

Although recovery usually is rapid and complete an occasional case passes into the progressive virulent type of the disease with involvement of bones subcutaneous tissues and internal organs including the brain

Sometimes the organism gains entrance through the skin or possibly through the tonsils Lesions of the glands of the neck have been described which simulate tuber culous adenitis

The extensive rapidly fatal cases of coccidioidal granuloma are analogous to re infection tuberculosis and often develop years after the initial exposure The lungs usually are infected sometimes as the only organ involved but more often as a part of a generalized disease that includes bones joints vertebrae subcutaneous tissues in ternal organs and brain The roentgeno graphic shadows are easily mistaken for tu berculosis but the presence of bone and sub cutaneous lesions should suggest coccidioidal granuloma actinomycosis or blastomycosis

Diagnosis—One should suspect coccidi oidal granuloma in any obscure disease originating in a native of the endemic area and in individuals who have visited such areas *C immitis* can be found in the sputum in the case of primary infection In the re infection type the organisms are present in the sputum in the subcutaneous abscesses and in the lesions of the internal organs Precipitins and complement fixing anti bodies are present in a high titer in the pri mary cases but low or absent in the gran ulomatous cases The coccidioidin skin test is positive except in certain terminal anergic patients

Coccidioidal granuloma must be differen tiated from tuberculosis syphilis glanders bacterial osteomyelitis epithelioma and other mycoses

Prognosis—The prognosis is excellent in primary pulmonary involvement good in the dermal and glandular types of the dis ease when they are a part of the primary infection but most grave in the generalized and meningitic types

Treatment—Most primary pulmonary infections heal rapidly in a few weeks with out specific treatment The primary cases which have persistent thin walled cavities present a difficult problem Winn advises that conservative treatment be followed at home and surgery be avoided except pneu mothorax for the occasional patient with hemoptysis

The chronic generalized type of disease is difficult to treat Potassium iodide and vaccine therapy have been disappointing The best results have been obtained by Jacobson who uses colloidal copper supple mented with injections of coccidioidin Col loidal copper in 5 cc doses is injected deep in the gluteal region every four to seven days for ten to twenty five doses The coccidioidin injections may serve to reduce the patient s sensitivity

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PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis is a chronic gran ulomatous disease and is quite similar in its clinical course to coccidioidal granuloma

At the present time the disease is con fined to South America where De Almeida has collected the reports of 255 cases The

sence of polymorphonuclear, eosinophilic and lymphocytic reaction It seems probable that the lesions in the various organs result from masses of cells blocking the capillaries and producing localized necrosis The most extensive lesions occur in the liver spleen lymph nodes bone marrow and lungs

Symptoms —Very little is known of the symptoms presented by the patient in the early stages of the disease because most cases have been diagnosed postmortem or only shortly before death The terminal picture is characterized by splenomegaly hepatomegaly emaciation irregular pyrexia leukopenia and anemia Not all patients present this complete syndrome the liver and spleen may not be enlarged the disease may be confined chiefly to the lungs or even to the skin as in the case studied by Hansmann and Schenken

Diagnosis —The disease should be suspected in cases of unexplained splenomegaly and hepatomegaly especially if accompanied by irregular fever and leukopenia and anemia Dodd and Tompkins diagnosed their case before death by finding the characteristic organism in the monocytes of the circulating blood Repeated blood cultures should be made employing dextrose agar Sternal bone marrow punctures may furnish material for both direct examination and culture In pulmonary infections the sputum should be cultured and also inoculated into mice

Prognosis —There are no known recoveries

Treatment —Nothing specific is known about treatment Potassium iodide ionized copper and x ray therapy have been ineffective Sulfadiazine should be tried or possibly gentian violet intravenously in daily doses of 5 mg per kilogram of body weight

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MONILIASIS

Definition —*Monilia* may produce acute or subacute infections of the mouth vagina, skin nails bronchi and lungs and occasionally a septicemia endocarditis or meningitis

History —The organism now known as *Monilia albicans* was discovered in oral thrush by Langenbeck in 1839

Etiology —The disease is found in all parts of the world at all ages in all races and in both sexes Oral thrush is most common in infants and in patients with wasting diseases Pregnancy and diabetes predispose to vaginal moniliasis Dermal lesions occur in bakers waiters fruit packers, bartenders and housewives whose hands are macerated from frequent soaking in water Poorly fitting artificial teeth predispose to infections of the tongue and mouth

Benham isolated both pathogenic and nonpathogenic strains of *Monilia* from normal skin and showed by animal experiments that *M albicans* is the only pathogenic species The various species of *Monilia* have been classified by Benham by Stovall and by Martin

Bacteriology —*Monilia* grow readily on Sabouraud s medium at room temperature or at 37° C and develop moist white elevated colonies with a distinct yeast like odor after two to four days incubation *Monilia albicans* is lethal for rabbits ferments certain sugars agglutinates in specific sera and forms typical chlamydospores on corn meal agar

Immunology —Positive skin tests of the tuberculin type are frequently present but are not diagnostic because they occur in normal individuals The immediate (twenty minutes) wheal like skin test occurs occasionally in all types of monilia infections but most frequently in patients with bronchial asthma

vomiting The patient has little or no fever and the pulse and blood pressure remain normal The disease often is mistaken for a rather chronic type of tuberculous meningitis *After several weeks or months* more severe symptoms and signs appear, such as neuroretinitis papilledema, strabismus nystagmus ptosis, diplopia ataxia or hemiplegia The patient ultimately becomes comatose and dies of respiratory failure

Diagnosis—The dermal, subcutaneous and glandular lesions may be diagnosed by routine biopsies and cultures on Sabouraud s medium The diagnosis of the pulmonary forms is made by growing the organism from the sputum In the meningeal form of the disease the spinal fluid pressure is increased and the spinal fluid usually contains 200 to 800 cells which are chiefly mononuclear The spinal fluid sugar is decreased The *Cryptococci* are present in small numbers and are readily mistaken for red cells or lymphocytes After centrifugalization the sediment from the spinal fluid should be planted on Sabouraud s medium and watched for three or four weeks Not infrequently the organism can be found by direct examination if a drop of the sedimented material is mixed with india ink

Prognosis—The prognosis is grave in all forms of the disease, especially the cerebral form which *until recently has been considered* inevitably fatal

Treatment—The local lesions are treated by surgical excision or drainage supplemented by local x ray therapy and potassium iodide by mouth (see Blastomycosis) Repeated lumbar punctures diminish the symptoms of patients with cryptococcosis of the central nervous system Recently Mar*shall and* Teed reported the recovery of a patient following intensive treatment with sulfadiazine

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HISTOPLASMOSIS

Definition—Histoplasmosis is characterized by emaciation splenomegaly, hepatomegaly, leukopenia, anemia and irregular pyrexia

History—In 1906 Darling in Panama, found round or oval parasites in *the* endothelial cells and monocytes of certain cases of splenomegaly He thought the organisms were protozoa and suggested the name *Histoplasma capsulatum* In 1934 Dodd Tompkins and De Monbreun isolated the organism from a typical clinical case in a child and found it was a fungus Earlier in the same year *Hansmann* and Schenken isolated a fungus from a patient with a refractory skin infection which later was found to be identical with the De Monbreun culture More than thirty cases have been diagnosed in this country in the past eight years

Etiology—Histoplasmosis has been found in Central America Java and throughout the United States All races seem susceptible both sexes are attacked at all ages but children seem to be relatively more *susceptible* than to other mycotic infections De Monbreun found a dog with a spontaneous infection

Bacteriology—The organism can be isolated directly from the blood from the sternal bone marrow or from tissues at necropsy by planting the material in dextrose agar or dextrose broth at 37° C Two *types of colonies appear a mycelial* type and a yeast like type The mycelial form is less pathogenic but when infection is induced by intraperitoneal inoculation in the mouse the organism reverts and the yeast form can be recovered

Pathology.—Histoplasmosis is primarily a disease of the reticulo endothelial system The organisms are found in the cytoplasm of circulating monocytes in the tissue phagocytes of the various organs in the lymph nodes bone marrow and in the endothelial cells of small lymph and blood vessels and capillaries There is a conspicuous ab

outlined in the section on Blastomycosis In some cases the patients have positive skin tests to *Monilia* vaccines and may not respond to the iodides until partial desensitization with vaccine has been effected Intravenous gentian violet in doses of 5 mg per kilogram of body weight each day or every other day for four to six doses sometimes cures massive pulmonary infections

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SPOROTRICHOSIS

Definition—Sporotrichosis is a chronic infection characterized by the formation of gumma like nodules abscesses and ulcers The lesions usually are confined to the skin and superficial lymph nodes

History.—Schenck in 1896 isolated a fungus later identified as *Sporotrichum* by E F Smith from a patient in Johns Hopkins Hospital The second case was described by Hektoen and Perkins in 1900 who named the fungus *Sporotrichum schenckii* The disease was recognized in France in 1903 by de Beurmann and Raymond and their organism was named *Sporotrichum beurmanni* by Matruchot and Raymond

Etiology—The disease occurs throughout the world but most often in males especially farmers laborers and horticulturists The primary lesion was on some part of the upper extremities in 90 of 102 cases Sporotrichosis occurs spontaneously in horses dogs and rats Meyer infected himself while working with an equine strain Benham and Kesten s transmission of the infection to carnations *with a culture isolated from man* suggests that plants may act as intermediate hosts

Bacteriology—The organism grows readily on Sabouraud s honey agar or on plain meat extract dextrose agar, at room temperature or at 37° C The growth appears after five to ten days incubation and shows small white colonies which slowly enlarge and then become brown or black

Immunology—Agglutinins and complement fixing antibodies may appear in the serum and occasionally the patient develops a tuberculin like sensitivity

Pathology—The gumma like nodules usually consist of a central abscess surrounded by granulation tissue with giant and epithelioid cells and a peripheral zone of connective tissue histologically resembling syphilitic tuberculous or other chronic inflammations In the living tissue *Sporotrichum* occurs as oval bodies of fairly uniform size 2 to 3 microns broad and 3 to 5 microns long

Symptoms—The primary lesion usually is in the skin and may appear as early as twenty days or as long as three months after the initial infection The primary lesion is a hard spherical elastic movable subcutaneous nodule and not adherent to the overlying skin It becomes attached to the skin which first becomes pink and then purplish and finally black and necrotic This lesion (sporothrix chancre) may persist for months Usually after a few days or weeks multiple subcutaneous nodules appear along the course of the lymphatic drainage These nodules are at first freely movable but later adhere to the overlying skin become reddened and ulcerate through to the surface discharging a small amount of thin pus The lymph vessels between the nodes may become so thickened they can be felt as hard cords

The clinical types of the disease have been classified by de Beurmann and Gougerot as (1) lymphatic (2) disseminated (3) epidermal (4) sporotrichosis of the mucous membranes (5) skeletal sporotrichosis and (6) visceral sporotrichosis In the rare disseminated gummatous form single or successive crops of nodes develop at intervals Forbus found only two reported cases in which the evidence of pulmonary involvement was in any way satisfactory

Precipitins and agglutinins usually but not always are present in pulmonary and generalized moniliasis

Pathology—Both budding cells and mycelial threads are found in scrapings from the dermal and mucosal infections In the lungs and other internal organs focal areas of necrosis are found which contain budding cells with or without mycelium Giant cells may or may not be present The cellular reaction is one of polymorphonuclear leukocytes, monocytes and lymphocytes

Symptoms—White patches in the mouth or vagina should suggest the possibility of *thrush* or *vaginal moniliasis*

Paronychial and *onychial* infections are fairly common

Dermal lesions in malnourished infants usually begin about the anus and over the inguinal or crural region and may be vascular, pustular or erythematous and squamous

Intertriginous moniliasis is rather common and may be seen at any age It is characterized by a primary erythematous vesicle or pustule which extends peripherally and forms plaques with irregular borders These are separated from the normal skin by heaped up accumulations of whitish epithelium

Dyshydrosiform eruptions may develop in individuals whose feet and hands perspire abnormally The lesions consist of discrete vesicles which resemble closely those seen in certain types of epidermophytosis

Generalized eruptions in patients subjected to continuous water bath therapy may develop over the palms nails axillae knees and genital regions Dark red infiltrated papules appear which become confluent and form large plaques with irregular borders

Glossitis occurs occasionally and may result in hypertrophied somewhat blackened papillae or the papillae may be replaced by a hard white patch

Bronchitis both the acute and chronic varieties result from bronchial infections The symptoms resemble those of bacterial bronchitis but the sputum usually is mucoid or gelatinous

Pneumonitis occurs as an acute or subacute process The lungs may show massive patchy consolidation in one or more lobes There is cough malaise fever and leukocytosis but usually the patients are less toxic than with bacterial infections The sputum is mucoid or mucopurulent and may contain blood

Diagnosis—The skin lesions are diagnosed by finding *Monilia* in the scrapings or on culture It is impossible to find *Monilia* in some of the vesicular lesions and it is probable that these are allergic reactions analogous to the 'ids' in epidermophytoses

The bronchial and pulmonary lesions are diagnosed by growing *M albicans* the one pathogenic species from the sputum Even *M albicans* may be an accidental contaminant from the mouth or bronchi or a secondary invader in tuberculosis carcinoma or some other mycoses If there are agglutinins in the patient s serum in a dilution of more than 1 to 80 the diagnosis of moniliasis probably is correct but agglutinins may not be present in the early weeks of extensive pulmonary infections

Prognosis—The acute dermal lesions respond well to treatment The recurrent type is more resistant The acute types of glossitis and stomatitis heal readily but the chronic type of glossitis may persist for years Patients with bronchial and pulmonary forms of the disease usually recover although occasionally the pulmonary form is fatal

Treatment—The cutaneous lesions should be kept dry especially those precipitated by excessive wetting Local applications of potassium permanganate (1 1500) or soaking in the solution for thirty minutes twice each day usually cures the dermal lesions If this is not successful mercurochrome in a 2 per cent solution or alcohol (50–70 per cent) should be applied daily Ointments such as chrysarobin (1–2 per cent) or crude tar (2–6 per cent) have been used The oral lesions usually respond to alkaline washes or to gargles with 1–10 000 gentian violet Potassium permanganate (1 1500) or gentian violet (1 10 000) douches are used for the vaginal lesions X ray therapy has been used successfully for onychia and paronychia If perleche does not respond to local treatment vitamins should be administered (riboflavin 10 mg daily pyridoxine 50 mg daily or yeast 15 Gm daily)

Bronchial and pulmonary moniliasis should be treated with potassium iodide as

are confined to the feet and legs but may be limited to the hands and arms In 1911, Pedroso of S10 Paulo Brazil isolated a pigmented organism from patients with verrucous lesions of the skin which was later named *Hormodendrum pedrosoi* Large spherical bodies dark brown in color are present in abundance in the verrucous lesions and grow readily on Sabouraud s medium

Pathology —The disease is very chronic and may last for years With the development of extensive fibrosis in the deeper dermal lesions the lymphatics are blocked and the patient develops an elephantiasis of the extremity

Treatment —Complete destruction of the lesion by surgical excision or electrotherapeutic methods would seem to be logical when the disease is diagnosed in its incipient stage Surgical amputation is not justifiable because the lesions rarely become severely infected and usually make sufficient response to medical treatment to leave the patient with a useful limb The internal treatment consists of large doses of potassium iodide up to as much as 1 to 9 Gm per day Iontophoresis with copper sulfate was employed with considerable success in the case reported by Martin Baker and Conant

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ASPERGILLOSIS

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David T Smith

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Diagnosis—The diagnosis is established by cultivating the organisms from the discharges or from material removed at biopsy The disease may simulate syphilis tuberculosis blastomycosis cryptococcosis glanders, tularemia leprosy *or pyogenic infections*

Prognosis—Uncomplicated sporotrichosis is rarely fatal, when untreated it persists *for months or years but* appropriate treatment usually is followed by rapid healing

Treatment—Potassium iodide should be given in slowly increasing doses up to 4 to 6 Gm or more daily If absorption of closed abscesses is slow, they may be punctured aspirated and injected with a weak solution of iodide Incision and curettage are to be avoided Ulcerated lesions may be painted with tincture of iodine and dressed with a solution containing water 500 cc potassium iodide 10 Gm and iodine 1 Gm The treatment should be continued for at least a month after apparent recovery

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MADUROMYCOSIS

(*Madura Foot*)

Maduromycosis or mycetoma is a chronic infection affecting principally the foot but in rare instances other parts of the body It is characterized by multiple abscesses and sinuses and the development of granulation and connective tissues

Bacteriology—Carter in 1860 proved that the disease was a mycosis and introduced the term mycetoma or fungus tumor The disease may be caused by any one of thirteen species of the genus *Actinomyces or any one of nineteen* species of molds belonging to two classes and eight genera (Gammel)

Etiology—The specific cause is contained in the white, yellow, deep brown or black granules which appear in the discharges from the affected region The disease is most common in males and in farmers or other individuals who come directly in contact with the soil

Pathology—The pathologic reaction is essentially the same regardless of the type of invading fungus There is local and general swelling of the parts affected with a corresponding degree of deformity In old chronic cases the skin is darkened and the surface studded with pitted scars open sinuses and nodular fungating elevations Dense masses of scar tissue are found in the healing lesions The abscesses connected with the sinuses are filled with mucoid fluid in which the characteristic granules are floating

Prognosis and Treatment—Maduromycosis does not heal spontaneously The disease continues to progress and the patients eventually die of secondary infection if the disease process is not eradicated by excision or amputation Sulfonamide therapy is a useful supplementary treatment

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CHROMOMYCOSIS

Chromomycosis or verrucous dermatitis is characterized by the formation of warty cutaneous nodules which through slow progressive growth become transformed into prominent papillomatous vegetations which may or may not ulcerate Usually the lesions

are confined to the feet and legs but may be limited to the hands and arms In 1911, Pedroso of São Paulo Brazil isolated a pigmented organism from patients with verrucous lesions of the skin which was later named *Hormodendrum pedrosoi* Large spherical bodies dark brown in color are present in abundance in the verrucous lesions and grow readily on Sabouraud's medium

Pathology —The disease is very chronic and may last for years With the development of extensive fibrosis in the deeper dermal lesions the lymphatics are blocked and the patient develops an elephantiasis of the extremity

Treatment —Complete destruction of the lesion by surgical excision or electrotherapeutic methods would seem to be logical when the disease is diagnosed in its incipient stage Surgical amputation is not justifiable because the lesions rarely become severely infected and usually make sufficient response to medical treatment to leave the patient with a useful limb The internal treatment consists of large doses of potassium iodide up to as much as 1 to 9 Gm per day Iontophoresis with copper sulfate was employed with considerable success in the case reported by Martin Baker and Conant

David T Smith

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MUCORMYCOSIS

Mucormycosis is a rare disease with clinical characteristics resembling aspergillosis Several cases of pulmonary mucormycosis have been reported The first authentic case in man was studied by Paltauf in 1885 The initial infection was in the lungs but metastatic abscesses developed in various organs before death The treatment is the same as for aspergillosis

DAVID T SMITH

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SPIROCHETAL INFECTIONS

SYPHILIS

Definition —Syphilis is a specific infectious disease of protean manifestations caused by the *Treponema pallidum* It may be acquired or congenital The *acquired form* is characterized by an initial sore and an early stage of invasion with relatively mild systemic disturbance and by eruptions upon the skin and mucous membranes After a variable interval there follows a late stage of specific granulomata connective tissue proliferation with destruction of parenchyma and disturbance of the function of various organs The *congenital form* is similar in its pathology except that there is no primary lesion and the late manifestations predominate

History —There are two opposing views concerning the antiquity of syphilis One is that the disease was introduced into the civilized world in relatively recent times by the returning sailors of Columbus and that it was spread throughout Italy in 1493 by the soldiers of Charles VIII It was about this time that the disease became a great scourge and spread rapidly over Europe The other view is that syphilis is a very ancient disease which has existed among civilized peoples since the very dawn of history Early Egyptian and Assyrian inscriptions as well as the bony changes found in mummies are cited as documents in evidence The controversy continues

The syphilis of the Middle Ages was virulent and widespread Its rapid propagation at this time was effected by various modes of personal contact and its venereal origin was not generally recognized Later syphilis came to be regarded solely as a venereal disease but the hard chancre the soft chancre or chancroid and gonorrhea were not distinguished for a long time They were differentiated by Ricord

Then there came in the nineteenth century a period when syphilis was studied largely in its dermatologic aspects Although the dermatologists of the day (Ricord Hebra Fournier and others) understood the general character of the infection the graphic appearances on the skin and mucous membranes seemed in their minds to dominate the clinical picture and to give the disease special dermatologic interest

In the early part of the twentieth century the conception of syphilis was greatly broadened and the disease gradually assumed a different clinical aspect Experimental study was facilitated by the discovery of Metchnikoff and Roux that syphilis can be transmitted by inoculation to the lower animals In 1905 Schaudinn made the epoch making discovery of the causative agent, the *Treponema pallidum* About a year later Wassermann devised the biologic reaction of great diagnostic value to which his name has been given In 1910 Ehrlich in his studies in chemotherapy succeeded in producing the highly potent remedy salvarsan (arsphenamine) Finally in 1913 the much discussed question of parasyphilitic disease was settled by Noguchi when he demonstrated the constant presence of the treponema in the brain of paretics As a result of these discoveries syphilis is now recognized as a general disease with protean manifestations For the first time its menace has been given widespread publicity and its spread is being combated by public health agencies everywhere

Incidence —The generally accepted estimate that, taking the population as a whole 10 per cent of adult Americans have syphilis is probably accurate but there are enormous differences For example of the private patients I see less than 1 per cent have syphilis and of the Negroes in the medical wards of the hospital more than 25 per cent are infected A good picture was given by Usilton and her associates in their studies of one of the largest American cities wherein it was revealed that 44 persons per ten thousand are constantly being treated for this disease and that of 15 000 who seek such treatment each year only 2500 have early syphilis

Etiology —The *Treponema pallidum* was first discovered by Schaudinn and Hoffman in the tissue fluids of an initial syphilitic lesion Subsequently its causative relation to syphilis was abundantly proved both by these investigators and by others Koch s

postulates have been fulfilled This treponema is a delicate spiral corkscrew' organism 6 to 20 microns in length actively motile and difficult to stain It is claimed the organism is polymorphous and that granular and other forms exist but this has not been substantiated It can perhaps best be classed among the protozoa

The parasite is found in abundance in the tissue fluids and secretions of the primary lesion During the early stages it is present in large numbers in the lymph nodes particularly in those nearest the initial sore Later it may be found in the roseola and other skin lesions as well as in the inner organs During the so called secondary stage it has been found in both blood and spinal fluid Treponemas have been demonstrated in the scars of syphilitic lesions long after healing The apparently healthy tonsils of untreated syphilitics have been shown to harbor the organisms in abundance In general it may be said that during early syphilis there is an invasion of the entire body so that treponemas are present in abundance in practically all of the organs in late syphilis the infection is more localized and smaller numbers of the organism are found in the parenchyma of the diseased organs Treponemas can seldom be found in the specific granulomas of the late stages but are encountered in relatively small numbers in the apparently healthy surrounding tissue They are found in greatest abundance in the tissues and organs of infants with congenital syphilis Outside the body the treponema dies quickly It is rapidly destroyed by ordinary soap

Modes of Transmission—Syphilis is most often transmitted by sexual intercourse but other forms of personal contact such as kissing the nursing of an infant by an infected wet nurse or the examination by the physician of an infected patient also spread the disease Although extragenital chancres may be found on any part of the body they are usually located on the lip and the finger Indirect contact such as comes from the use of a common instrument by glass blowers musicians etc or a common drinking cup is sometimes a mode of transmission The extragenital chancre is particularly dangerous because its true nature is often unrecognized and no precautions are taken to prevent transmission In localities where syphilis appears to be endemic and to afflict almost the entire population the extragenital method is probably the most common form of transmission Infection most often results from contact with the chancre or mucous patch although it can be derived from almost any syphilitic lesion The earlier the lesion the greater the chance of infection

The treponema is believed by many to produce invariably an initial sore at the point of entrance, but there is good evidence that at times it passes through the apparently unbroken skin without producing a chancre

Congenital syphilis is transmitted by the mother If the infection originally comes from the father the mother is first infected and then after acquiring the disease she transmits the treponema through the placenta to the fetus

Morbid Anatomy—The primary sore or chancre is a local inflammatory lesion characterized by infiltration with lymphocytes and plasma cells, these cells accumulate in the tissues and around the blood vessels and block the lymph vessels This obliteration of arteries veins and lymph vessels is especially characteristic of syphilis Interference with the blood supply leads to retrogressive changes Finally only a scar remains

Even before the chancre has fully developed the treponema invades the neighboring lymph channels and thence finds its way into the general circulation Local lymphangitis and lymphadenitis are therefore early lesions The roseola and other skin manifestations which develop a little later represent a reaction of the skin to the presence of the treponema

Other so called secondary lesions may be found in any of the organs Obliterative arteritis as well as phlebitis and round cell infiltration accompanies all the early changes At this stage the fixed tissues with the exception of the vessels are not extensively destroyed

In late syphilis on the contrary not only are the vessels involved but there is extensive destruction of parenchyma with an overgrowth of fibrous tissue This chronic interstitial inflammatory reaction presents

no peculiarly characteristic features except perhaps the invariable obliterative arteritis and phlebitis Diagnosis is often facilitated, however by the presence of the gumma—the characteristic lesion of late syphilis

The gumma is a granuloma or conglomeration of granulomas in the formation of *which an infiltration of lymphocytes and* a few epithelioid and plasma cells plays the chief role connective tissue proliferation obliterative endarteritis phlebitis and necrosis also take place The gumma is often soft in the center and exudes semisolid debris It may be of almost microscopic size or a large tumor several centimeters in diameter After it breaks down scar tissue usually forms

The most characteristic histologic feature of syphilis is the involvement of the blood vessels This consists at first of an intense round cell infiltration in the adventitia and in the *vasa vasorum* which may spread evenly along the vessel wall or may appear as irregularly placed nodules All syphilitic lesions are said to have their beginning in the walls of the blood vessels In their studies of experimental syphilis Cunningham and his associates were impressed by the phagocytic activity of the mononuclear cells of the tissues They concluded that these cells play an important part in the resolution of syphilitic lesions

The Course of Syphilis—From the very beginning syphilis is a general disease in which the entire body is involved The treponema enters through the skin or mucous membrane and produces at the point of entrance a characteristic tissue reaction—the chancre or papule An abrasion or other lesion favors but it is not essential for infection, for the organism can unquestionably enter the apparently unbroken skin

The chancre appears within from ten to ninety days after infection usually after about three weeks Even during this *first incubation period* before the ulcer can be seen the infection begins to spread throughout the body The treponema early gains entrance to the lymph vessels and invades the blood stream

After the appearance of the chancre there is a *second incubation period* of variable length (usually six weeks to six months) during which there are no symptoms except, possibly, secondary anemia and enlargement of the regional lymph nodes Important changes however are taking place at this time The treponemas are making good their invasion of the tissues and the body is developing defensive reactions which *lead* to the presence of antibodies in the blood

The end of this secondary incubation period is marked by the appearance of typical *eruptions of the skin and mucous membranes* This has been termed the secondary period of syphilis The eruption quickly disappears with treatment, but in untreated cases may persist a long time with gradual change During this stage treponemas may be found in the blood stream and cerebrospinal fluid and in a large number of patients cellular changes provide evidence of cerebrospinal involvement The other evidences of general involvement are described below

The eruption and other symptoms of this period may be so slight as to escape notice or may be absent altogether Many observers think that when this is the case the infection finally develops into the most malignant late type but their belief is doubtless due in part at least, to the fact that the asymptomatic type escapes treatment and consequently develops unhindered Treatment at this time causes a disappearance of all symptoms and if therapeutic measures are prompt energetic and sustained relief is as a rule, permanent Occasionally the eruption may recur once or twice in the same areas and even a *chancre redux'* may appear During this early period syphilitic processes are no doubt also taking place in the internal organs but they are relatively benign and produce few clinical signs

At the end of the secondary period especially in patients who have been inadequately treated there usually ensues a so called *latent period* This in turn is followed by the *tertiary* or *late period of visceral syphilis* The latent period may persist for only a few weeks or for twenty or thirty years It usually lasts for five to seven years The late manifestations which are deep seated and destructive may involve any of the organs and often endanger the patient's life Included among them are many ner

vous manifestations notably paresis and tabes dorsalis

This classical division of the course of syphilis into three stages is arbitrary and does not accord fully with our present understanding of the disease The secondary eruption may appear while the chancre still flourishes tertiary visceral manifestations may be produced by gummas during the period of florid secondary syphilis and the secondary period may merge imperceptibly into the tertiary stage or be missed entirely More rational therefore is the division of the disease into two stages early syphilis which includes the primary lesion and the so-called secondaries and late or visceral syphilis Although the dividing line between the two stages is not always sharp certain features of each warrant this distinction The *early stage* is characterized by the presence of a large number of treponemas in the lesions by the prompt response to treatment by lack of response to the administration of iodides and by the tendency of the lesions to heal without scars *Late* or *visceral syphilis* is characterized by the presence of a small number of organisms in the lesions by extensive destruction of parenchyma by the formation of gummas and connective-tissue proliferation by ready response to the iodides and by the formation of scars

Symptoms —In the following pages syphilis will be discussed as a continuous general infection with two types of manifestation the one occurring early and the other as a rule late

Acquired Syphilis —The *chancre* develops at the site of entrance of infection after an incubation of from ten to ninety days usually within about three weeks As a rule it is on the genital organs It appears first as a small papule which soon erodes into a reddish ulcer often covered by a grayish yellow exudate This is usually somewhat elevated but not excavated is distinctly circumscribed and has little or no areola of inflammation It is important to remember that the often described hard or shotlike consistency of the chancre cannot usually be detected for one or two weeks after onset The chancre may first appear as a simple erosion without induration The classical *hunterian chancre* is deeply ulcerated with a raised (not excavated) border and a cartilaginous consistency On the other hand the initial lesion may never ulcerate but remain merely a papule Most patients have only one chancre but when two mucous surfaces come in contact the lesion may in rare instances be multiple It is rarely painful and may, consequently pass unnoticed If not contaminated with chancroidal infection the chancre usually heals without treatment in four to six weeks Phagedenic ulceration sometimes occurs in very debilitated persons or when the lesion is both a chancre and chancroid (See *Diagnosis*) The chancre leaves a scar which usually persists several months The so-called *chancre redux* is caused by organisms which remain

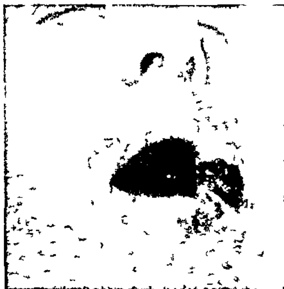


Fig 32 —Chancre of the lip (Courtesy of Dr Andrew L. Glaze)

in this scar Extragenital chancres may appear almost anywhere on the body—the finger lip eyelid tonsil nipple and tongue being its most frequent sites

A chancre is always accompanied by involvement of the lymph vessels and swelling of the regional lymph nodes which become palpable about three or four weeks after infection They are discrete and hard Unless the infection is mixed they do not suppurate

General Symptoms —While the chancre is disappearing and during the second incubation period the patient experiences a few vague symptoms There is usually moderate anemia and swelling of the general

lymph nodes Toward the end of this period just before the eruption symptoms of a more pronounced nature appear, many of which are common to all bacterial invasions The secondary anemia with pallor increases About a third of the patients have a low-grade fever which is often intermittent There is more or less physical and mental depression Pains in the bones and joints are frequent and sometimes severe The patient may complain of cardiac palpitation arrhythmias and other circulatory disturbances *On the other hand, he may feel surprisingly well* As the rash appears the severity of all these symptoms increases The fever is more constant and the temperature is perhaps higher the lassitude is more noticeable, and the patient may lose weight There is headache and pain in the bones and joints especially at the insertions of the tendons The spleen may or may not be palpable Icterus is frequent, and occasionally there is recognizable enlargement of the liver Iritis, and inflammation of various nerves particularly of the optic and auditory nerves may occur at this time Exaggeration of the reflexes is often noted, and rarely there may be a genuine syphilitic meningitis This stage is said to coincide with the most widespread distribution of the treponema throughout the body

THE SKIN AND MUCOUS MEMBRANES — The eruption of syphilis is manifold in character and can simulate practically any skin disease *Certain characteristics are however* common to all syphilitic skin manifestations they are usually symmetrical when papular the eruption is often arranged in circles or segments of circles which follow the distribution of the blood vessels they are often polymorphic consisting of two or more types of eruption at the same time, and unless irritated or otherwise complicated they do not cause pain or itching There are three main types of syphilitic eruption the macular papular and tubercular

(A) THE MACULAR ERUPTION —The macular eruption or roseola ordinarily is the first to appear It is seen usually on the abdomen and chest *the face often escapes* The rash may be nothing more than a faint diffuse blush or may consist of clearly defined rose-colored macules of varying size The dilated capillaries which produce *this* eruption contain large numbers of treponemas and the *blood taken from a roseola spot* or the fluid which exudes from the skin on injury, is highly contagious The roseola disappears within one or two weeks Another type of macular eruption often appears a little later, but may develop at the same time The macule of this type is slightly elevated persists longer than the other, is copper colored and in fading, often leaves a transiently pigmented spot or a faded area

(B) THE PAPULAR ERUPTION —The size of *the papule* varies greatly The lesion consists of the infiltration of small areas which are at first generally distributed over the body but later tend to become localized particularly around the genitals and anus In such locations the papules are inclined to become broader and to assume a wart like character They are then called *condylomata* Papules may appear on the palms of the hands or the soles of the feet as slight depressions When the scales which cover them are removed they are seen to have a reddish coppery color They are indurated and tend to crack open and ulcerate These *palmar syphilids* may develop in the late as well as in the early stages Papules occasionally destroy the nail bed and lead to a syphilitic onychia and paronychia which is most refractory to treatment The hair often drops out sometimes in patches giving a moth eaten' alopecia

The most characteristic persistent and *infectious of all syphilitic eruptions* the *mucous patch* is papular in character It develops on the mucous membranes of the mouth tongue tonsil prepuce and vagina as a slightly elevated glistening circumscribed area with a depressed center It is free from induration and is usually covered with a white or yellowish exudate These patches often coalesce to form large irregular areas They may persist for months and may continue to recur for many years

Papules occasionally suppurate and give rise to a pustular eruption This seldom occurs early and may be considered a more severe lesion than any of those already described The pustules tend either to dry up and become covered with brownish red crusts or to break down and form large ulcers Several varieties are described one *resembles acne* another *variola* there is a

third form called *impetigo syphilitica* and a fourth known as *ecthyma syphiliticum* in which there is extensive suppuration and ulceration

(c) THE TUBERCULAR ERUPTION—The tubercular or nodular syphilid often develops during an intermediary stage between early and late syphilis its histology being more typical of the latter condition This lesion consists of small discrete elevated nodules of a bluish red or ham color which tend to appear in circles and spreading at the periphery to unite and form serpiginous and other configurations As the nodules disappear they leave an atrophic brownish area which later becomes white In the more severe forms the nodules tend to become confluent When they appear late in the disease they often ulcerate They may persist many years

True *gummas* appear in the skin and subcutaneous tissues during late syphilis They often coalesce and ulcerate and thus produce large areas of necrosis The exudate from such an area dries and forms a crust continued exudation leads to the formation of another crust beneath this yet another and so on until a crust of many layers appears Other lesions may appear in the mouth throat or nose at any stage of the disease The tonsils frequently and less often the larynx are subject to these processes A characteristic feature of the mouth lesions is their tendency to recur and persist for many years They are highly contagious

There is no sharp dividing line between the early and the late skin lesions of syphilis The essential difference is that the latter are more local in character more chronic more liable to ulcerate and much more destructive than the early manifestations

THE BONES—During the early stages of syphilis the patient often complains of *pains in the bones* The headaches and neuralgias of syphilis are often due to involvement of bone it is possible as the result of vascular obliteration for necrosis and caries of the cranial bones to take place even in the early stages although at this time lesions in the bones are rarely demonstrable It is in late syphilis that the bone lesions are most apparent and more destructive Periostitis particularly of the long bones is frequent It is usually accompanied by pain redness and diffuse swelling The lesion may become absorbed but often stimulates the formation of new bone of extreme hardness as in the characteristic *saber shin* (periostitis of tibia) Exostoses are also common *Gummas* frequently form in the bone during late syphilis Destruction of the bones of the face and nose are often the result of such gummatous processes *Syphilitic dactylitis* characterized by a peculiar smooth bluish swelling of the phalanges sometimes occurs *Involvement of the vertebrae* may lead to pain on movement stiffness or deformity The pains of syphilitic bone disease are more intense at night and are said to be often relieved by exercise

A true *arthritis* may be an early manifestation of syphilis This may suggest tuberculosis or when of an acute polyarthritic nature rheumatic fever In late syphilis several types of monarthritis occur Involvement of the knee joint which may cause the formation of a *tumor albus* is difficult to distinguish from tuberculosis

THE CIRCULATORY SYSTEM—Involvement of the heart and aorta by the spirochete is frequent In their studies of 1000 syphilitic patients Cochems and Kemp found cardiovascular syphilis in 10.8 per cent of the women and 13 4 per cent of the men with a gross incidence of 12 7 per cent These figures are in essential agreement with those of other investigators

Early in the disease various cardiac disturbances may take place—tachycardia bradycardia and arrhythmia The heart is easily excited and quickly exhausted Undoubtedly early syphilitic myocarditis does occur but there is some question as to how often the above described condition represents true myocarditis Later gummas and interstitial inflammatory changes appear in the myocardium A gumma of the bundle of His with the threat of sudden death is a common cause of Stokes Adams syndrome Fibrous replacement of the myocardium as the extension perhaps of a process beginning in the coronary arteries is also common The symptoms are the same as those of myocardial disease from other causes except that cardiac failure may come with considerable abruptness and that disturbances of rhythm are relatively rare

Syphilitic aortitis which is often limited

to the thorax and usually begins near the root of the vessel, is a common disease, but unfortunately when uncomplicated it presents no recognizable signs, significant roentgenographic appearances are also wanting It frequently leads to aneurysm

Aortic insufficiency, which often follows aortitis pursues a variable clinical course The cor bovinum the water hammer pulse the murmur along the left border of the sternum, and the evidences of myocardial failure are described elsewhere in this book The characteristic electrocardiographic signs listed by Blackford and Smith are left axis deviation, defective interventricular conduction, low voltage of the T wave and deviation of the ST segment The sudden onset of cardiac failure, precordial pain and respiratory distress without edema are, according to the *same authors*, signs of *ominous* prognostic significance

THE RESPIRATORY ORGANS —In early *syphilis*, mild disturbances in the upper air passages are frequent and cause hoarseness and coughing Later deeper and more destructive processes occur Single gummas or more frequently, diffuse gummatous infiltrations develop and often break down into deep seated ulcers Hoarseness and aphonia commonly result Such syphilitic processes can as a rule be distinguished from tuberculosis by the relative paucity of subjective signs There is most danger when the epiglottis and larynx are involved for edema and inflammatory swelling may cause complete *closure and death from suffocation* Ulceration may destroy the laryngeal cartilages

Syphilis of the lung has long been considered a rare disease but evidence is now accumulating which shows that it is more frequent than has been generally supposed Cough with expectoration (sometimes bloody), loss of weight and a variable fever —symptoms which are identical with those of pulmonary tuberculosis—*are the usual* manifestations The physical signs except perhaps for their location also suggest phthisis *Roentgenologic* signs are sometimes fairly characteristic and can be recognized by the fact that the process is largely limited *to* one part of one lung usually the middle or lower portion With proper treatment the prognosis is excellent

THE DIGESTIVE ORGANS —(A) THE ESOPHAGUS —Syphilis of the esophagus is rare and usually represents extension of the infection *from some neighboring structure*

(B) STOMACH —Early in the disease functional gastric disturbances are frequent The patient *complains of lack of appetite and of* a sense of pressure in the epigastrium At times there is regurgitation of food A large *percentage of patients have lowered acidity* perhaps anacidity or achylia Little is known of the actual gastric pathology at this stage and it has been suggested that much of the distress and disturbance of function is due to disease of the vagus nerve Although involvement of the stomach may occur at any time after invasion by the spirochete becomes general outspoken syphilis of this organ is usually a late manifestation of the disease The existence of syphilis of the *stom*ach as an etiologic entity has been questioned but this was answered by Harris *and Morgan when they recovered* the organism from the gastric lesion and a regional lymph node Eusterman describes three types of cases (1) The most frequent is the type in which epigastric pain comes on immediately after eating and is made proportionately worse by an increase in the solidity of the food or in the amount of fluid taken The capacity of the stomach becomes greatly reduced vomiting is frequent and partial starvation results *Dumb*bell and high hour glass stomachs are seen Sixty three per cent of the cases were of *this group (2) The pseudo cancer type* was represented by 15 per cent of the cases There is a gradual onset with mild pains one half hour or more after eating relief obtained from food and alkalis is inconstant and incomplete (3) The ulcer type with typical ' pain food ease ' was encountered in 22 per cent of the cases

(C) THE INTESTINES —Syphilis of the intestines is rare In early syphilis a diarrhea *occasionally occurs which* if untreated may become chronic This symptom is encountered more frequently however in the later stages of the disease Such catarrhal diarrhea is particularly severe in cachectic individuals Gummata occasionally form in the intestinal wall they may break down into ulcers which in healing produce circular *scars and* stenosis Gummas may also appear in the rectum

but according to Ault stricture of the rectum due to syphilis is rare The picture revealed by the proctoscope is not typical

(D) THE LIVER —Invasion of the liver is frequent and symptoms referable to this organ are encountered often both early and late The mild icterus suggestive of catarrhal jaundice which occasionally appears either before or during the efflorescence may be an extension of the disease from the duodenum or a true exanthem of the bile passages The presence of jaundice with or without other symptoms in a patient with early untreated syphilis usually points to acute benign syphilitic hepatitis which disease according to Waugh clears up rapidly (usually with a mild Herxheimer s reaction) when small doses of arsphenamine are given There may also be enlargement of the spleen and fever A rapidly fatal disease of the liver apparently identical with acute yellow atrophy may develop within a year after infection

The late manifestations of syphilis of the liver are the formation of gummas and chronic interstitial inflammation either alone or together Gummas may be miliary (often multiple) or they may reach the size of large tumors They usually begin in the immediate neighborhood of a blood vessel which they eventually destroy Fibrous tissue with scars usually results but other retrogressive changes may lead to localized fatty or amyloid degeneration As a rule gummas of the liver do not break down but when they do an irregular perplexing fever often ensues

Chronic interstitial hepatitis begins with a cellular infiltration around the blood vessels which extends and leads finally to the production of thick fibrous tissue Gradually there develops a cirrhosis of the liver in which the parenchyma is replaced by this newly formed connective tissue Bands of tissue often divide and distort the liver so that it assumes an abnormal often bizarre shape which serves to distinguish this form of cirrhosis from the ordinary type described by Laennec although the latter disease may sometimes occur as the result of long continued syphilis alone or in association with alcoholism This type of cirrhosis develops slowly over a period of years It may exist for a long time without producing symptoms although, as a rule definite signs are present The liver is often nodular It may be larger than normal or, because of the constricting bands, may undergo atrophy in one part and hypertrophy in another Ascites hematemesis and other signs of portal obstruction are evident Jaundice and albuminuria are usually present as well as severe pain and a low grade fever With gummas alone the prognosis is relatively good, but with chronic interstitial inflammatory changes treatment avails little

(E) THE PANCREAS —Indurative pancreatitis occasionally occurs as a late syphilitic process The parenchyma is replaced by connective tissue and the organ becomes hard usually larger than normal and in thin individuals can occasionally be palpated This type of interstitial pancreatitis is however rarely recognized during life Gummata also occur Syphilis of the pancreas is often associated with syphilis of the liver Syphilitic diabetes mellitus is rare Joslin reports that sixteen out of 1000 diabetics gave a positive Wassermann reaction

THE KIDNEYS AND URINARY TRACT —Mild albuminuria with or without casts is a frequent accompaniment of early syphilis and is usually associated with no other symptoms of renal involvement During this period there may develop however a true acute syphilitic nephritis with edema and other symptoms identical with those of the usual glomerular nephritis The treponema and not mercury or arsenic as is sometimes suggested is probably the causative agent A little later there occasionally appears a degenerative disease identical in its clinical features with nephrosis Its onset may be rapid or insidious The disturbance is distinguished by marked edema pallor prostration headaches and scanty excretion of urine containing much albumin and a sediment composed in part of degenerated kidney epithelium hyaline and granular casts and certain characteristic lipoid bodies These lipoid bodies appear in the urinary sediment as small droplets which when viewed in a polarized light seem to be divided by a black cross into four highly refractile sections They serve to distinguish this disease from the nephritis of a similar character which occasionally follows the ex

cessive use of mercury The prognosis is good under treatment

In its later stages, syphilis sometimes gives rise to a nephrosclerosis which may follow the disease just described or develop gradually without previous symptoms It has the following distinctive characteristics there is often no elevation of blood pressure, polyuria is usually absent, the water concentration test shows little impairment of the ability of the kidneys to excrete nitrogen and salts and there is moderate albuminuria with an abundance of hyaline casts and occasionally lipoid bodies With treatment the outlook for arresting the disease is good

Gummata occasionally appear in the kidneys, but cannot be recognized during life unless they reach the size of great tumors

The urinary bladder sometimes gives trouble in early syphilis It presents the symptoms and cystoscopic appearances of chronic cystitis or tuberculous cystitis In late syphilis ulcers may appear as the result of broken down gummas

THE TESTICLES AND OVARIES —Animal experiments have shown that the treponema grows with especial ease in the testicle a fact corroborated by clinical experience *The semen in early syphilis may contain* treponemas, even when there is no clinical evidence of testicular involvement Orchitis, a fairly frequent and characteristic manifestation of syphilis may occur early although it appears as a rule two or three years after primary infection It is usually double The testicle is swollen hard and rarely painful The epididymis is involved *in only about one half the cases* This chronic interstitial inflammatory process may destroy the parenchyma and produce finally a small sclerosed testicle but only certain parts of the organ may be involved and some parenchyma left to function Syphilitic orchitis may be confused with gonorrhea tuberculosis *or carcinoma* Pain fever and involvement of the epididymis are characteristic of *gonorrhea* pain degenerative changes and the presence of *tubercle bacilli* in the urine characterize *tuberculosis* while *carcinoma* grows faster is usually unilateral and has an even contour Gummata with the eventful formation of fistulae occasionally involve the testicle

Little is known of syphilis of the ovary It probably leads to menstrual disturbances and eventually to amenorrhea and sterility

OTHER ORGANS OF INTERNAL SECRETION — The *thyroid gland* is occasionally enlarged in early syphilis most often when the disease has been untreated Late in the disease it may undergo a chronic inflammatory change which results in fibrosis and may cause symptoms of pressure or lead perhaps to myxedema

Syphilitic involvement of the *hypophysis* and *its neighboring tissues can give rise* to *diabetes insipidus* or to the endocrine disturbance known as *dystrophia adiposogenitalis* Syphilis may destroy the *adrenals* and induce Addison s disease

THE NERVOUS SYSTEM —Syphilis of the central nervous system is difficult to classify because from neither an anatomic nor a clinical standpoint are the several types clearly defined They occur together overlap and merge into one another For purposes of description the following grouping is the best

1 Meningeal syphilis
2 Cerebrospinal syphilis
   (a) Vascular
   (b) Parenchymatous

(A) MENINGEAL SYPHILIS —The *meninges* are involved early and with great constancy Estimates as to the frequency of such disturbances in early syphilis which are based upon examination of the spinal fluid vary from 50 to 100 per cent Dreyfus found changes in the spinal fluid of 80 per cent of patients with syphilis The vast majority of such patients give no clinical evidence of meningitis yet the character of the cells in the lumbar fluid shows that a true meningitis though of low degree exists The spinal fluid undergoes some elevation of pressure there is pleocytosis chiefly of mononuclear cells with occasional polynuclear and plasma cells and the globulin content is markedly increased The Wassermann reaction of the spinal fluid may be negative at this stage although that of the blood is positive These signs of meningeal involvement disappear *quickly if treatment is thorough* but they may remain for a long time in poorly treated or neglected patients Their chief importance lies in the fact that if they are dis

regarded a small percentage of the subjects will years later, develop tabes or paresis

Less often there occurs a syphilitic meningitis with outspoken clinical signs This disorder may appear very early even before any other general manifestations are evident but it usually develops simultaneously with the skin symptoms during the first generalized invasion of treponemas There is manifest inflammation of the meninges with connective tissue proliferation and the formation of new granulation tissue which dips into the brain substance and thus establishes a true meningo-encephalitis As usual there is involvement of the smaller arteries and veins The meningeal lesions are not evenly distributed but are confined to more or less restricted areas Basal meningitis which involves chiefly the region of the optic chiasma and the space between the peduncles is the most frequent form The coverings of the cord are often involved in the region of the posterior columns (tabes) The symptoms depend largely upon the location of the inflammatory process The preponderance of basal meningitis accounts for the frequency of syphilitic paralysis of the cranial nerves Involvement of the region of the hypophysis may lead to *diabetes insipidus* If the cortex is attacked psychic disturbances headaches vomiting aphasia and perhaps jacksonian epilepsy may follow There may be delirium coma or convulsions The onset of epilepsy in a patient thirty or more years of age is always suggestive of cerebral syphilis With early sustained treatment the prognosis of early syphilitic meningitis is good

Syphilis of the dura mater is usually an extension of the disease from the other membranes or from the bone Two types have been distinguished a *pachymeningitis haemorrhagica interna* and a *pachymeningitis hypertrophica* Both are serious

(B) The Brain and Cord.—Syphilis of the brain most often appears as part of a syphilitic meningitis—meningo encephalitis *Involvement of the blood vessels* as repeatedly stated is a prominent feature in all syphilitic pathology especially here for it is most often through the vessels and the accompanying perivascular infiltration that the disease is spread to the brain The changes are essentially interstitial and affect the nervous tissue only indirectly At the same time treponemas may penetrate into the brain substance and, on reaching the nerves themselves give rise to a true parenchymatous cerebrospinal syphilis Luetic *endarteritis obliterans* often interferes with the cerebral circulation and leads to softening of the brain These processes seem to have a preference for the interpeduncular space at the base of the brain and for certain cortical areas Both may be involved With involvement of the base disturbance of the cranial nerves is frequent The optic nerve the extrinsic nerves of the eye and the auditory nerve are most often affected It is said that an optic neuritis is much more common in early syphilis than is ordinarily thought With syphilis of the cortex there may be headache psychic disturbances jacksonian epilepsy and various motor symptoms While the several forms of cerebrospinal syphilis just described usually occur early in the disease often in the first year they may also appear late As a rule however the late manifestations of this type are due to gummata or usually to combined gummatous and fibrous processes which arise in the meninges and extend along the vessels to the brain or cord The symptoms depend upon the location of the tumor

The prognosis of these interstitial processes is good if treatment is early and energetic This is not true however when the treponema has extensively invaded the brain substance and is not within easy reach of bismuth and arsenic When the treponemas invade the nerves themselves degeneration of these structures follows and irreparable damage is done

If such invasion is extensive it must be called *parenchymatous cerebrospinal syphilis* Outstanding examples of this group are paresis and tabes dorsalis The symptoms of the parenchymatous forms are similar to those of the meningeal and vascular forms but vary of course according to the location of the process There are three features which are said to characterize the symptoms of cerebrospinal syphilis (*a*) their extreme variability and disappearance with recurrence at short intervals (*b*) their multiplicity and involvement of widely

separate areas, and (*c*) their association with structures at the base of the brain

Dementia paralytica and tabes dorsalis are placed in a category of their own because, being a late effect of the localization of the treponema in the parenchyma of the brain or cord, each presents a fairly well-defined symptom complex. The two are often combined, with varying emphasis on the one or the other, and tabes is today sometimes looked upon merely as a part of the exceedingly variable syndrome of neurosyphilis, but for purposes of description each can be regarded as definite clinical entity. These will be discussed elsewhere. (See *Syphilis of the Central Nervous System*.)

Inadequate or irregular treatment is an important factor in the development of *syphilis of the central nervous system*. This was clearly shown in the studies of Wile and his associates, and in the report of O'Leary.

THE EYE AND THE EAR.—The eye is frequently involved in syphilis and sometimes offers the only recognizable symptom. A plastic *iritis* often occurs early, and *iridocyclitis* perhaps a little later. An especially severe form of iritis, the *iritis papulosa*, may appear relatively early or as a late manifestation. Retinitis develops in late syphilis; the retinal vessels show characteristic changes and hemorrhages may occur. The optic nerve is not infrequently congested in early syphilis, while in the late disease there is often an optic neuritis or neuroretinitis which if untreated may lead to optic atrophy. The apparent hopelessness of this last is seen in the studies of Lehrfeld and Gross. Of 570 patients with optic atrophy who received no treatment 74.9 per cent were blind in less than three years and all were blind at the end of five years; of those who received the most aggressive treatment, including fever therapy and subdural injections, 28 per cent were blind in less than three years and all were blind at the end of eight years.

Otitis media is often an early manifestation of syphilis. It differs but little from other forms of otitis media except in the unusually rapid loss of hearing, the pains in the bone, and the fact that the disease is usually bilateral. In late syphilis the process may lead to destruction of the internal ear. Deafness follows involvement of the auditory nerve.

OTHER INDEFINITE LATE MANIFESTATIONS.—Certain other indefinite symptoms of a general nature are prone to occur in late syphilis. A low grade fever, otherwise difficult to explain, should always excite a suspicion of syphilis. The fever of pneumonia and of typhoid fever has been known to continue long after apparent recovery and then promptly subside as soon as a positive Wassermann reaction was discovered and antisyphilitic treatment instituted. The emotional instability which we call "neurasthenia" occasionally occurs in late syphilis without other signs of disease. An indefinite state of ill health with malaise, anemia, and lack of initiative may also be the result of so called "latent syphilis."

Syphilis in the pregnant woman, no matter what the stage of pregnancy, demands energetic treatment. The Wassermann test should be done twice during every pregnancy, at the third and eighth months. If treatment is begun before the fifth month and is sustained, the chances are good that a healthy child will be born. The pregnant syphilitic woman tolerates antisyphilitic treatment well and the outcome is favorable in direct proportion to the amount of such treatment she has received. The fetus responds to arsenic in the usual manner.

Congenital syphilis is transmitted only through the mother. If the disease originally comes from the father, he infects the mother and she, through the placenta, infects her offspring. The duration of the infection in the parent has an important influence upon the likelihood of transmission. Fournier showed that the disease is transmitted usually during the first three years after infection. The danger then gradually lessens, so that five to ten years after the initial lesion syphilis is as a rule no longer transferable by the father. The mother, however, may even after twenty years infect her child. According to estimates quoted by Whipple and Dunham, of 683,000 syphilitic persons under observation in the United States more than 60,000 acquired the disease from the parent, this in spite of the fact that, as was shown in the Cooperative Clinical Studies, congenital syphilis is a preventable disease.

The *symptomatology of congenital syph*

ilis does not differ materially from that of the acquired disease except that there is no primary sore and the late manifestations appear much earlier sometimes indeed simultaneously with the usual early symptoms Those children who at birth show outspoken evidence of syphilis and who usually die within the first few weeks of life have a true treponema septicemia This is manifested by the bullous eruption of the skin the fissures about the angles of the mouth and nose, the characteristic nasal discharge to which the name *snuffles* has been given the enlargement of the spleen and liver the bony changes about the joints the poor state of nutrition and the faulty development. The congenitally syphilitic children who are conceived at a later period of the parental disease and who at first show no recognizable symptoms a little later usually appear unmistakably syphilitic. *Snuffles* is one of the most constant symptoms *Eruptions* macular or papular appear upon the skin most often on the buttocks or the face the macules are of a coppery brown color with well-defined edges Instead of this type of rash there may be a mere erythema or an eczema The papules tend to become confluent and to cover large areas especially on the hands and feet and around the mouth In the severe cases bullae appear which burst and may produce large sores The skin and mucous membranes of the lips may undergo a peculiar diffuse infiltration called *cheilitis diffusa* Fissures appear at the corners of the mouth when these are deep and ulcerated they are called *rhagades* In healing they leave linear radiating scars which are peculiarly characteristic of congenital syphilis Syphilitic *onychia* is common and the hair may fall out These children are apt to be unusually restless at night and are said to have a peculiar harsh high pitched cry

Teeth—*Hutchinson's teeth* provide the most characteristic feature of congenital syphilis The central incisors of the permanent teeth most often the upper are notched on their free borders as if a half moon shaped piece had been chipped out moreover they are usually peg-shaped that is smaller at the free end than at the gums Additional defects involving peculiarities of form size and spacing of the teeth are seen but these last are common to other states of malnutrition and are not peculiar to syphilis

The Blood—Anemia is frequent Josephs states that severe anemia appearing during the first three months after the neonatal period is always suggestive of congenital syphilis

The Digestive Organs—The liver is often extensively involved and is usually enlarged It is subject to the same lesions observed in acquired syphilis *Diffuse hepatitis* may develop about the time of puberty and lead to cirrhosis of the liver The *spleen* also is often enlarged Both the *pancreas* and the *kidneys* are subject to chronic interstitial inflammation in late congenital syphilis and both may be retarded in their development

Bones—Characteristic of congenital syphilis is an *osteochondritis* which attacks the centers of ossification between the shaft and epiphyses of the long bones The normally thin zone of calcification becomes very much widened and irregular a condition easily recognized in the radiogram Swelling and pain in this area are the chief symptoms The lower end of the femur is the region most often attacked

The Nervous System—In congenital syphilis the central nervous system is subject to the same changes as the acquired form In addition the retarded and abnormal cerebral development may lead to epilepsy hydrocephalus or idiocy It is said that juvenile dementia paralytica develops in about 1 per cent of all patients with congenital syphilis

The Eye and the Ear—Later in the disease often in adult life there is an *inflammation of the cornea* an interstitial keratitis which is seldom seen in the acquired disease but is especially characteristic of congenital syphilis It may occur at any time although the onset is most often between the ages of six and fifteen years Of 247 congenitally syphilitic children studied by Lennarson and Jeans 43 per cent of those more than two years of age had interstitial keratitis Of 1010 patients with late congenital syphilis studied by the Cooperative Clinical Group this condition was the principal initial diagnosis in one third of the cases Untreated the disease leads to cloudiness of the cornea and frequently to blindness Optic

neuritis and chorioretinitis also occur Optic atrophy is less frequent Involvement of the ear is common and may lead to deafness

The *recognition* of congenital syphilis is not always easy, the apparently normal infant of a syphilitic mother may have the disease The presence of the well known triad Hutchinson's teeth interstitial keratitis and deafness merely tells of irreparable damage already done The diagnosis must be made earlier and for this purpose correlation of many factors is often necessary the appearance of the infant, the demonstration of the disease in the parents serologic tests of both infant and cord the roentgenologic appearances of the bones and the finding of spirochetes in the placenta For testing the blood of suspected infants Faber and Block advise quantitative rather than qualitative methods

Diagnosis—The chancre can often though not invariably be distinguished from the chancroidal ulcer by the following characteristics the former has a definite period of incubation while the latter has not the typical chancre presents a clean slightly elevated circumscribed ulcer the edges of which are not excavated the chancroidal ulcer exudes an abundant pus has an inflammatory areola and is elevated with undermined edges the former rests upon a hard base of almost cartilaginous consistency while the latter is soft The only sure diagnostic criterion is the finding of the treponema This is not difficult in a dark field preparation made of serum expressed from a relatively fresh untreated chancre or aspirated from a neighboring lymph node One group of experienced workers report positive dark field examinations in 94 per cent of seronegative primary syphilis and in 90 per cent of the genital lesions of secondary syphilis Failure to find the organism however should not be accepted as final

Later in the disease the history may be of importance particularly if it tells of a primary sore or secondary rash or in a woman of repeated miscarriages Experience has taught, however that a negative history *should* be accorded little consideration The physical examination may uncover significant findings such as the scar of a chancre evidences of old skin lesions persistent enlargement of the lymph nodes or bony changes such as the distinctive saber shin

Serum Reactions—Of great importance in the diagnosis of syphilis and in the evaluation of treatment are the Wassermann complement fixation reaction and the several flocculation tests As a rule the reaction is not immediately positive and cannot be obtained until about the time the so called secondary symptoms develop usually the eighth or ninth week after infection After this a positive Wassermann reaction is the most constant of all signs of syphilis and in the vast majority of cases it remains positive until influenced by treatment With the rarest exceptions it always indicates active syphilis—active even though it may not produce symptoms In addition this reaction serves as an excellent guide to treatment, for it has been demonstrated that the majority of patients who are adequately treated experience a reversal of a hitherto positive Wassermann reaction within a year usually within six months A weakly positive test (1 plus) occurring after a series of negative reactions in early syphilis warns of approaching relapse, the spinal fluid should immediately be examined

The flocculation tests (notably of Kline or Kahn) have come to enjoy equal favor with the complement fixation test The American Serological Conference concluded that for both the blood and the spinal fluid the clinician can place equal value upon either test efficiently performed This conference reported approximately 100 per cent of positive reactions in untreated secondary syphilis and 63 to 84 per cent of positive reactions in late syphilis with varying treatment It was found that frequently in leprosy and sometimes in malaria, a false positive reaction was obtained

Seroresistance (Wassermann fastness) can be said to exist in early syphilis when at the end of six months of continuous treatment the serum reaction is still positive According to Moore and Padget this can be regarded as a manifestation of persistent foci of organisms or of progressive activity and as presumptive evidence that treatment has been inadequate or irregular in a *large* proportion of such cases the spinal fluid will reveal involvement of the neural axis In late syphilis seroresistance as indicated by a

positive reaction at the end of a year of continuous treatment has a different significance According to authors just quoted it can be regarded as an integral part of the manifestations of many late forms of the disease or as evidence of the persistence of well established immunity

The *spinal fluid* should be examined invariably in both early and late syphilis Asymptomatic neurosyphilis is of frequent occurrence and its prompt recognition may prevent the later development of serious trouble In spite of its lack of specificity the increased cell count is in the presence of a syphilitic infection a finding of the utmost importance as an index of involvement of the nervous system early in the course of the disease' Patients so characterized are peculiarly disposed to the subsequent development of the more serious forms of neurosyphilis At any stage of the disease a positive Wassermann reaction in the spinal fluid indicates active cerebrospinal syphilis and if the reaction remains positive long the patient is fortunate if he escapes paresis or tabes An increase in the globulin of the spinal fluid and a positive colloidal gold reaction with its characteristic curve are both of diagnostic significance

Prognosis—Syphilis can be cured Much depends however upon the promptness with which treatment is instituted and the fidelity with which it is continued The ease with *which cure can be accomplished is in inverse* ratio to the age of the infection If begun within the first few weeks or months after infection sustained treatment usually means an early and assured cure After two or three years cure is more difficult while in cases of ten or twenty years duration complete eradication of the infection is extremely difficult and often impossible The lesions of early syphilis usually heal without causing loss of function but in late syphilis with deep seated lesions and extensive destruction of parenchyma there can never be complete restoration of function Chronic syphilis is refractory to treatment because of the persistence of pathologic processes beyond the reach of medication For the same reason congenital syphilis does not yield readily to therapeutic measures

Prophylaxis—The sure way to escape syphilis is to avoid exposure Immediately after exposure the disease can generally be prevented by the prompt and thorough application of calomel ointment to the contaminated parts (calomel 3 parts, lanolin 1 part benzoinated lard 2 parts) Spirochetes placed on the intact genital mucosa of rabbits have been found after one hour to be buried within the crypts and after two hours to have penetrated the deeper tissues To be effective therefore chemical prophylaxis should be applied early preferably within an hour after exposure

Treatment—*General*—The patient himself as well as the disease requires treatment If he has fever he should be kept in bed and other symptoms of a general or specific nature must be combated with appropriate remedies Great attention should be paid to hygiene Alcohol should be avoided worry and overwork prevented as far as possible and sufficient sleep and recreation specifically prescribed A simple rational diet should be ordered The teeth should receive the best of care Repeated examinations of the urine and frequent physical examinations should be made Every patient no matter what the circumstances should in the beginning be told of the nature of his infection and should be warned of the tediousness of successful treatment The physician must have his confidence and his firm allegiance Otherwise the necessity for treatment will not be sufficiently appre*ciated and failure may result If the patient* is married the wife or husband as the case may be must be informed of the situation and due precautions taken to prevent transmission of the disease

Specific—Unlike many other infections syphilis is not self limited If the patient is to escape its harmful effects thorough continuous treatment is necessary True a few patients with early syphilis get well following meager therapy but this is exceptional To offer any assurance of success treatment should conform to the following specifications (1) it should be instituted early (2) it should be sustained and without interruption and (3) it should be long continued

As soon as the diagnosis is made even though the disease is yet in the seronegative stage treatment should begin for the longer this is delayed the more difficult it is to ef

fect a cure The "Cooperative Clinical Studies" indicated that treatment begun in the primary though seronegative, stage possesses a superiority of curative outlook of about one third over that begun in the secondary stage This superiority of early treatment becomes still more striking as the later stages are approached This is well illustrated in the studies of syphilis of the heart and aorta by Moore and his coworkers who conclude that adequate treatment for early syphilis almost certainly protects the patient against subsequent cardiovascular syphilis

Continuous treatment is necessary The 'Cooperative Studies just quoted demonstrated that uninterrupted medication is infinitely superior to the intermittent treatment in vogue in the past Among cases treated with arsphenamine alone, the continuous method secured the reversal of the blood Wassermann reaction by the end of a year in 91.2 per cent whereas the intermittent scheme of treatment with arsphenamine alone and rest intervals of a month or more secured only 58 5 per cent of reversals, and irregular treatment with arsphenamine alone secured only 9 3 per cent of Wassermann reversals to negative within a year Essentially the same proportions appear in discussing the serologic results with arsphenamine and heavy metal It is believed that the vast majority of failures in the treatment of syphilis notably in its early stages are due to the rest interval rather than to any peculiarity of the infecting organism or of the patient

Treatment should be prolonged It has been demonstrated that prolongation of continuous treatment for more than a year enhances enormously the patient s chances for complete recovery Much longer periods are often necessary especially if treatment is begun late

Three groups of drugs are of value in the treatment of syphilis the arsphenamines certain heavy metals (bismuth and mercury) and the iodides The members of the first two groups are spirocheticidal and tend directly to eradicate the infection while those of the last group promote the resorption and removal of the late manifestations of the disease The opinion has recently been expressed however that the iodides are not as indispensable as was formerly thought, and that the same effects are possibly better accomplished by arsenical or bismuth compounds

Arsphenamine and neoarsphenamine, directly or after conversion in vivo to some related compound are both strongly spirocheticidal in the earlier stages these drugs cause the rapid disappearance of the syphilitic manifestations Both are equally effective in the late stages also and one of them, with the occasional substitution of bismuth should be used throughout the course of treatment Both are administered intravenously They deteriorate when exposed to the air and each ampule therefore should be examined for leaks before use Only freshly distilled water is to be employed for preparing the solution, it should be administered with absolute asepsis and in sufficient dilution In the case of arsphenamine the neutralization of the dissolved salt should be exact and to permit completion of the chemical reactions the solution should stand a few minutes preferably thirty minutes and not longer than three hours before use In the case of neoarsphenamine however the solution should be administered immediately after preparation The dose of arsphenamine is 0 2 to 0 6 Gm that of neoarsphenamine 0 2 to 0 9 Gm Arsphenamine is the more potent drug of the two and is to be preferred but neoarsphenamine because of its ease of preparation is much more widely used For those cases in which intramuscular injections are necessary *sulfarsphenamine* is best The drug should be dissolved in 1 to 2 cc of sterile distilled water and injected at weekly intervals into alternate buttocks until ten doses have been given

Mapharsen a cleavage product of arsphenamine is a potent antisyphilitic agent and has the advantage of producing fewer reactions Reports tell of satisfactory administration of this drug to patients who had previously experienced gastro intestinal upsets nitritoid reactions and other untoward effects from the arsphenamines The recommended course consists of twelve intravenous injections of 0 03 to 0 06 Gm each given at five day intervals

Tryparsamide is of value in the treatment of cerebrospinal syphilis, but is not recom

mended for other forms of the disease It should never be given unless facilities are available for examination of the fundi and visual fields by a competent ophthalmologist It is administered in doses of 1 to 3 Gm

Bismuth is superior to mercury in therapeutic effectiveness It should be used in conjunction with the arsphenamines or their derivative marpharsen An insoluble compound such as bismuth subsalicylate suspended in oil (0.2 Gm of the metal) injected intramuscularly at weekly intervals is generally preferred Water soluble compounds such as iodobismitol may be given for their quicker effect when the arsphenamines are contraindicated but they have the distinct disadvantage of requiring more frequent administration two to three times a week Sobisminol in the form of Sobisminol Mass is effective when given orally in capsules containing each 150 mg of metallic bismuth four to six capsules daily Only an exceptionally intelligent person however will continue persistently and faithfully to take oral medication for the prescribed period The subsalicylate given intramuscularly at weekly intervals is best

Mercury is seldom used today because it is less effective than bismuth When used the inunction method is best The dangers incident to its irregular absorption and accumulation must always be kept in mind

Potassium (or *sodium*) iodide is believed to be of value in all except the very earliest infections Apparently the iodides have no spirocheticidal effect but they facilitate the healing of gummas and other destructive lesions of late syphilis The drug should be given by mouth in doses of 10 to 40 grains daily

The Untoward Effects of Treatment— Arsphenamine dermatitis an exceedingly disastrous complication is much more likely to occur during the first course of treatment and is more frequent in patients who are receiving simultaneous arsenical and heavy metal therapy Statistics indicate that patients who are treated by the well established routine method are less susceptible than those who are treated by individualized methods Epstein states that the incidence of exfoliative dermatitis would be greatly reduced if before treatment with arsphenamine all patients with late syphilis were prepared by treatment with heavy metal Itching of the skin during the period of treatment may be a warning of approaching dermatitis and should be looked upon as a symptom of grave significance, it should suggest the abandonment of the arsphenamines Dermatitis is always a contraindication to the use of these drugs Jaundice even acute yellow atrophy of the liver and serious damage to the kidneys and bone marrow may follow arsphenamine therapy The nitritoid crisis is an immediate reaction which is accompanied by a flushing of the neck and face injection of the conjunctiva choking sensation palpitation backache and perhaps edema of the lips and tongue with occasional collapse Idiosyncrasy of the patient or perhaps faulty technic is responsible Adrenalin given before treatment may prevent this crisis Patients with cardiovascular syphilis may experience sudden collapse and even die during arsphenamine treatment a catastrophe which can usually be prevented by the restriction of medication to very small doses or the substitution of neoarsphenamine (0 1 to 0.3 Gm) for the older drug

The Herxheimer reaction which may follow a first injection of arsphenamine is a 'flare up of an old syphilitic lesion and is of serious significance only when a vital structure is involved

To prevent such reactions the Cooperative Clinical Group offers the following suggestions (1) Before beginning treatment search for a history of idiosyncrasy allergic tendencies skin irritability (especially eczema and seborrhea) focal and intercurrent infections liver damage and pregnancy (2) Before each treatment inquire regarding (*a*) gastro intestinal reactions and (*b*) the condition of teeth and gums and examine at least the eyes (jaundice) face (dermatitis) mouth (salivation purpura) flexures of the elbows (dermatitis) wrists and ankles (purpura) Take the temperature (3) Make the first dose of any drug not more than half of full dose (4) Pull back on syringe pistons (*a*) in intravenous injections to be sure of entry in vein and (*b*) in intramuscular injections to be certain a deep vessel has not been entered (5) Inject intramuscularly into the inner angle of the upper outer quadrant of the buttock and massage long and

A SCHEME OF TREATMENT FOR EARLY SYPHILIS (MOORE AND ASSOCIATES MANAGEMENT OF SYPHILIS IN GENERAL PRACTICE SUPPLEMENT No 6 TO VENEREAL DISEASE INFORMATION U S PUBLIC HEALTH SERVICE)

DAY* OR WEEK	ARSPHENAMINE GM	INTERIM TREATMENT	BLOOD WASSERMANN REACTION	REMARKS
Day				
1	0 3–0 6		1	Arsphenamine dosage for first 2 injections at level of 0 1 Gm for each 25 pounds of body weight Average subsequent dosage 0 4 Gm men 0 3 Gm women In average patient all lesions heal rapidly and blood serologic test becomes negative during first course If arsphenamine cannot be used substitute 8 to 10 doses 0 3 Gm silver arsphenamine or 10 to 12 doses 0 6 Gm neoarsphenamine This applies also to subsequent courses
5	0 3–0 6			
10	0 3–0 6			
Week				
3	0 4			
4	0 4			
5	0 4			
6	0 4			
7	0 4			
8		Bismuth 4 doses 0 2 Gm and KI or Ung Hg and KI		
9				
10			1	If mercury is used note overlap of one week at end of first and start of second arsphenamine courses
11				At this point a few days without treatment may be dangerous (neurorecurrence)
12	0 4		1	Arsphenamine starts bismuth stops Watch for provocative Wassermann reaction after first dose of arsphenamine
13	0 4			
14	0 4			Try to prevent lapses in treatment especially at this early stage
15	0 4			
16	0 4			
17	0 4		1	
18–23		Bismuth 6 doses or Ung Hg and KI		*Bismuth is better than mercury* Use it if possible Examine cerebrospinal fluid at about this time
24	0 4			
25	0 4			
26	0 4			
27	0 4			
28	0 4			
29	0 4			
30–37		Bismuth 8 doses or Hg and KI		
38	0 4		1	
39	0 4			
40	0 4			
41	0 4			
42	0 4			
43	0 4		1	Patients with seronegative primary syphilis may cease treatment here if blood serologic test has always been negative
44–53		Bismuth 10 doses or Ung Hg and KI		Note that bismuth or mercury courses are now gradually getting longer—4 6 8 and now 10 weeks
54	0 4		1	The average seropositive primary or early secondary patient should have at least 5 courses of arsphenamine
55	0 4			
56	0 4			
57	0 4			
58	0 4			
59	0 4		1	
60–69		Bismuth 10 doses or Ung Hg and KI		It is safer to finish treatment with bismuth or mercury rather than with arsphenamine
70–122		Probation no treatment	6–12	Blood serologic test every month if possible at least every other month
123	Complete physical and neurologic examination spinal puncture and if possible fluoroscopic examination of cardiovascular stripe. Thereafter yearly physical examinations blood serologic test every 6 to 12 months If the 2 spinal fluid examinations above are negative this need not be repeated later			

well (6) Inject intravenous solutions slowly through a small needle not faster than 0 1 Gm per minute for arsphenamine (7) Permit only a light meal before and after an arsenical and prescribe a mild cathartic the morning after (8) Examine urine biweekly and (9) give calcium freely With these suggestions is included not only the admonition that alcohol be interdicted but also the advice that carbohydrates be restricted and proteins and fats permitted in liberal amounts I doubt the wisdom of restricting the carbohydrates Animal experiment would indicate the advisability of giving large doses of ascorbic acid say 50 to 100 mg daily

Plan of Treatment —*Early syphilis* should be treated from the very beginning with arsphenamine and bismuth which should be continued without interruption (see accompanying schedule) Not less than twenty and seldom more than thirty injections of arsphenamine are required No rest period should be permitted until a full year of treatment has been completed Furthermore treatment should always be continued for one year after the blood and spinal fluid Wassermann tests have become negative and remained so

Blood tests should be made at the beginning and end of each arsphenamine course and the spinal fluid should be examined before the arsphenamine treatment is discontinued A negative blood test should not be permitted to interfere with the previously arranged schedule

Latent and *late syphilis* cannot be treated in quite such a routine manner because many circumstances related to the patient s condition demand individualization of the treatment The routine above outlined however is generally applicable Intermittent treatment with rest periods is not so objectionable in late as in early syphilis Treatment should not be too intensive lest damage be done to important structures The urine should be watched and great caution should be observed in giving the arsphenamine in syphilis of the liver In cardiovascular syphilis neoarsphenamine is the drug of choice but it should be given in very small doses Bismuth also should be given If aortic insufficiency is present prolonged treatment with this metal should precede the use of neoarsphenamine if there is cardiac failure the arsphenamine should be withheld until competency has been restored If there is early involvement of the central nervous system arsphenamine and bismuth should be given the former being administered in an intensive manner and at intervals of five rather than seven days later tryparsamide under proper control and perhaps fever therapy should also be given Visceral syphilis demands the arsphenamine and bismuth therapy described above plus liberal amounts of the iodides In general it can be said that treatment of late syphilis should be less intensive than that of early syphilis and without regard for the Wassermann reaction continued over a period of two years

Massive arsenotherapy, designed to cure syphilis in a few days is still an experimental procedure but it apparently holds promise The slow intravenous drip method first proposed by Hyman and his co workers has been slightly revised and the procedure used today is to give a total of 1200 mg (1 2 Gm) of Mapharsen throughout a period of five days This amount of the drug is administered by one of three methods (*a*) by slow intravenous drip in which 2000 cc of solution is given continuously each day for periods of seven to ten hours each (*b*) by rapid intravenous drip in which 1000 cc of solution is given continuously each day in periods of one to three hours each and (*c*) by multiple daily injections of small amounts of solution given with a syringe A recent progress report states that the treatment is effective and that the toxic manifestations are mild and infrequent with the exception of toxic encephalopathy the incidence of which is higher with all intensive methods than with the standard methods of treatment Other less highly intensive methods designed to shorten the standard treatment to a period of a few weeks or months are also being studied Further reports will be looked for with interest

Even more startling is the proposed one day cure Artificial fever (106° F) is maintained for about ten hours and during this period the patient is given arsenotherapy by multiple injections Satisfactory results have been reported but the efficacy of the method and its safety is still under investigation

The treatment of congenital syphilis

should not be too aggressive in the beginning When it is recognized early, medication should begin with the administration of mercury with chalk 0 015 Gm to 0 03 Gm (¼ to ½ grain) three times daily for one or two weeks or with injections of bismuth *subsalicylate in doses of 0 001 Gm* per kilogram given at weekly intervals until three doses have been given Then sulfarsphenamine, beginning with 0 005 Gm per kilogram gradually increased to 0 01 Gm per kilogram should be given intramuscularly at weekly intervals for ten weeks Following this the child should be given forty to fifty intramuscular injections each of sulfarsphenamine and bismuth arranged in alternating courses each of ten weekly injections In interstitial keratitis the iodides are contraindicated and recourse should be had to intensive arsenotherapy combined with fever therapy in all but the mildest cases Fever therapy in this condition either in the form of malaria or the hypertherm combined with the administration of riboflavin is surprisingly efficacious Combined with tryparsa*mide therapy it is also of value in juvenile* paresis

Cure —Syphilis can as a rule be cured if treatment is begun early and is continued sufficiently long without interruption Un*fortunately there are no known conditions* the fulfilment of which will warrant the physician in giving final assurance of cure *but for his guidance the following criteria* have tentatively been adopted If during the twelve months immediately following the completion of a full course of treatment (see accompanying schedule) the patient receives no antisyphilitic medication develops no lesions and exhibits repeatedly negative Wassermann reactions and if at the end of that period a thorough examination including careful scrutiny of the cardiovascular and nervous systems and always the spinal fluid shows no progress of the disease then he may tentatively be regarded as cured But he must not be dismissed entirely He should be examined from time to time at gradually lengthening intervals for the rest of his life

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YAWS

Definition —Yaws is a specific disease caused by a spirochetal organism *Treponema pertenue* It is largely limited to tropical countries and is characterized by an initial cutaneous lesion which is *followed* by a multiple papular granulomatous skin eruption and in some instances by late destructive lesions of the skin *and bones* Lesions of the soles of the feet are especially common Among synonyms for the disease are frambesia tropica pian *(French)* bouba (Spanish American) and parangi (Ceylon) Many others are listed by Hermans (1931)

History —The earliest reliable accounts of yaws now available date to the Seventeenth Century Since Negroes were brought from Africa to the West Indies as early as 1510 it cannot be determined whether yaws was introduced into the Americas *through* this means or whether the disease already existed among the native tribes Undoubtedly it was prevalent among slaves imported from Africa and by the Eighteenth Century yaws had become a *serious* problem on plantations in the West Indies

Etiology —The spirochete of yaws (*Treponema pertenue*) was *first* described by Castellani in 1905 soon after the discovery of *T pallidum* by Schaudinn The organism *measures from* 8 to 20 microns in length and about 0 2 micron in diameter It has six

to fourteen closely placed spirals and morphologically is indistinguishable from the spirochete of syphilis It is best seen in the fresh state by dark ground illumination The organism stains with difficulty

Among laboratory animals *Treponema pertenue* is pathogenic for monkeys and rabbits and gives rise to subclinical infection in mice rats and related species (Schobl 1928 Pearce and Brown 1925) At ordinary temperatures the organism survives for only a few hours when removed from a living host It cannot be grown on artificial media When stored at the temperature of solid carbon dioxide (—78° C) it remains virulent for several years (Turner 1938)

Epidemiology —*Distribution and Prevalence* —Yaws as an endemic disease is practically limited to the tropics It is particularly common in equatorial Africa the West Indies parts of India Ceylon, the Philippines the Dutch East Indies and throughout the entire group of Southern Pacific Islands Endemic foci occur in parts of Brazil and Colombia in South America and in several countries of Central America Only sporadic cases have been reported from North America and Europe The disease is not distributed uniformly however even within the tropics The situation in Jamaica as found by the epidemiologic studies of the Jamaica Yaws Commission (Turner Saunders Kumm and others 1935–1937) is interesting and may be representative of that in other countries In that country the distribution of yaws is very uneven Areas of high prevalence lie within a few miles of communities in which it is rarely encountered and there is a close correlation between its prevalence and certain environmental factors Where yaws is common there is practically always found a heavy rainfall and a fertile moisture holding soil supporting an abundant vegetation

It is principally a disease of rural peoples the lowest social and economic groups showing the highest attack rate The disease is most prevalent among Negroes and East Indians but cases are observed among mulattoes whites and Chinese In the South Pacific Islands it is Melanesians and Polynesians who are most affected There is no clear evidence of racial immunity

Yaws is usually acquired in childhood but no age is free from the risk of infection In one community in Jamaica (Bath) prevalence rates rose from 20 per cent among all children under five years of age, to 75 per cent among those ten to fourteen years of age In that area 33 per cent of the general population under twenty years of age showed active yaws lesions at the time of the study while among persons over that age 14 per cent showed active lesions Approximately 90 per cent of all persons found to have infectious lesions were under twenty years of age

Transmission —Yaws can be transmitted by direct person to person contact but it is probable that nonbiting insects also play a role in the spread of the disease There is no evidence for the existence of an animal or avian reservoir The initial yaws lesion which develops at the point of implantation of the spirochete is frequently observed at the site of a previous injury and is located on the lower extremity in the majority of cases Sexual transmission rarely occurs Transmission from mother to child *in utero* has not been established

Since earliest times the possibility of transmission by insects has been recognized Studies in Jamaica (Kumm and others 1935–1936) indicate that in this country a small gnat *Hippelates pallipes* is a likely mechanical vector This insect abounds where yaws is prevalent and in general is scarce where the incidence of yaws is low It feeds avidly on human sores and abrasions and has a predilection for lesions about the feet and legs When the fly feeds on an infectious yaws lesion material containing *Treponema pertenue* is taken into the esophageal pouch where the spirochetes may retain active motility for seven hours Upon feeding again which the fly may do repeatedly within the space of a few hours material from the esophageal pouch or diverticulum is regurgitated onto the new lesion Actively motile spirochetes can be demonstrated in this vomit drop The spirochete apparently undergoes no life cycle in the fly for all traces of it disappear after about forty eight hours Rabbits have been infected by having Hippelates flies feed first on infectious human lesions and then after an interval on wounds of the back or scrotum of normal rabbits

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After several months retrogression of the generalized lesions may begin The smaller lesions heal and the large frambesiform lesions tend to become smaller and less numerous but it may be many months be fore they have entirely disappeared Even then relapses are not uncommon so that infectious types of lesions may be present off and on for several years after the onset of the disease Eventually a stage of latency is usually reached but this stage may likewise be interrupted at intervals by the occur rence of more bizarre types of lesions in which *Treponema pertenue* cannot be readily demonstrated

After several years have elapsed skin lesions similar to the syphilitic gumma may occur These so called 'late lesions are characterized by tissue destruction and ulceration often involving large areas of skin and subcutaneous tissue *Treponema pertenue* cannot be found but other types of spirochetes notably *Spirochaeta refringens* may be present Healing often leads to ex tensive scarring which if located in the region of a joint may lead to contractures

Lesions of the soles of the feet are very common and account for a good deal of the disability from the disease Two types which may occur alone or together are recognized One type consists of one or more eroded papules somewhat analogous to the fram besiform lesion of the skin Instead of pro truding above the plantar surface however the papule lies at the base of a small open ing in the sole and is exquisitely tender Serum from these lesions is usually rich in *Treponema pertenue* Like other infectious lesions plantar papules are observed most commonly in the first years of the disease

The other type of plantar lesions consists of widespread hypertrophy stripping or fissuring of the superficial layers of the sole giving rise to a curious mottled pattern very characteristic of yaws There is usually no ulceration and *Treponema pertenue* cannot ordinarily be demonstrated Plantar hyper keratosis may occur at almost any period during the course of yaws it has been ob served in patients soon after development of the generalized rash as well as twenty years or more after infection

Bones—In the Jamaica series bone lesions were observed in about 15 per cent of all patients showing active manifestations On the basis of x ray changes two types are recognized although not infrequently both types are present simultaneously In the one type periosteal proliferation, similar to that seen in syphilis is the most prominent feature In the other type areas of rarefac tion or destruction in the shafts of the long bones are observed These areas are round or oval and usually multiple with a sur rounding zone of increased density Clin ically the patient complains of pain in the affected region and there may be tender ness and swelling of the overlying soft parts (Maul 1918) The bones of the forearms legs and hands seem most often to be affected, involvement of the skull pelvis and spine is rare Both periostitis and osteitis may occur either in association with infec tious skin lesions or in later years after the generalized skin lesions have healed

Other Yaws Lesions—Among the less common but more spectacular lesions of yaws are gangosa goundou and juxta articular nodules In *gangosa* the cartilagin ous and bony structures of the nose are partially or completely destroyed by a late ulcerative process Cutaneous leishmaniasis may cause somewhat the same picture *Goundou* is an egg shaped paranasal en largement arising from the superior maxil lary bone The tumors may be sufficiently large to interfere with vision (Strong and Shattuck 1930) *Juxta-articular nodules* are firm freely movable painless subcutaneous fibroid tumors situated in proximity to a joint

Differential Diagnosis—A case of yaws with typical generalized lesions cannot easily be confused with any other disease Individ ual lesions may resemble those of secondary syphilis or cutaneous leishmaniasis but when the case as a whole is considered little dif ficulty should be experienced Demonstra tion of the treponeme in skin lesions serves to differentiate yaws from all conditions except those of the syphilis group Late ulcerative lesions of yaws are often indis tinguishable from the tertiary lesions of syphilis The late effects of yaws ulcerative lesions contractures partial amputation of digits may resemble the lesions of leprosy

Pathology —The most characteristic lesion of yaws is the cutaneous papule or frambesioma Histologically, the lesion shows marked epithelial hyperplasia, with elongation of the papillae There is exudation of leukocytes on or near the surface with many lymphocytes and plasma cells in the dermis With silver stains the spirochetes of yaws are constantly found in large numbers in the epidermis and more superficial dermis There is no evidence that the spirochete is phagocytosed by polymorphonuclear leukocytes or histiocytes The smaller



Fig 33 —Yaws in a child showing generalized frambesiform lesions

skin lesions such as scaly macules and folliculopapules show these changes to a less degree The late ulcerative lesions of yaws are very similar histologically to syphilitic gumma Although the gross and microscopic picture of the frambesioma of yaws is fairly characteristic histologic criteria for the differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis are in general unreliable (Williams 1935 Ferris and Turner 1937) Lesions of the bones occur but no histologic studies have been reported The occurrence of visceral lesions in yaws is still debated, although evidence is accumulating that the aorta is sometimes involved (Choisser 1929, Chambers, 1936 Weller 1937) With possible rare exceptions the central nervous system is not affected

Symptomatology —*Skin* —Within two to eight weeks after infection the initial or primary lesion appears at the point of implantation of yaws spirochetes This lesion is a granuloma and may develop into a large cauliflower like growth from which *Treponema pertenue* can be recovered (Fig 33) There is accompanying enlargement of the regional lymph nodes The initial lesion usually persists for several months and heals with scar formation

During the first weeks of the disease *Treponema pertenue* gains access to the blood stream and symptoms attributable to generalization of the organism soon become manifest These consist of widely distributed skin lesions often enlargement of the superficial lymph nodes bone and joint pains and in some cases clinically recognizable lesions of these structures Mild constitutional symptoms such as low grade fever loss of appetite and slight loss of weight may occur but in many cases the general health of the individual is not materially affected About this time blood serologic tests similar to those employed in the diagnosis of syphilis (Wassermann Kahn Eagle Hinton) become positive, increase rapidly in titer and remain positive for many years unless rendered negative by specific therapy

The generalized rash may comprise at first only scaly macular lesions More commonly however from the beginning the rash is polymorphous comprising scaly macules folliculopapules papules and most prominent of all large granulomas—the yaw or frambesioma which is characteristic of this disease As the disease progresses the frambesiform lesions become more numerous and larger the patient with a fully developed generalized frambesiform rash presents an arresting picture one which can scarcely be confused with any other disease The individual lesion stands out from the skin level like a giant wart measuring 0 5 to 4 cm in diameter The surface of the lesion which may be covered by a crust is granular like the surface of a raspberry—hence the name frambesia Serum from the lesion

by mouth should not be used unless the more efficient drugs are unavailable Late skin lesions as a rule respond promptly to the usual drugs but the more chronic lesions of the skin and bones are often refractory and may require local surgical treatment

In the countries of high prevalence effectual control of yaws depends upon reducing the attack rate by bringing about a decrease in the source of infection *i.e.*, the infectious cases in the community through treatment The control measures instituted by the Jamaica Yaws Commission comprise the following First a survey of a given area for the purpose of detecting all infectious cases was made by sanitary inspectors then treatment of these cases with six weekly injections of either neoarsphenamine or bismuth and finally, close observation of the community so that new infections which arose could be treated promptly Since over 90 per cent of the infectious cases were among persons under twenty years of age it was to this part of the general population that control measures were directed By these measures it was possible to reduce the attack rate of yaws by at least 80 per cent (Turner Saunders and Johnston 1935 Saunders 1937)

THOMAS B TURNER

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GANGOSA

Gangosa is the term applied to a chronic ulcerative and destructive lesion involving the soft parts and cartilaginous portions of the nose The destructive process may extend to the bony structure of the nose the nasopharynx and the cutaneous tissue about the nose and mouth The lesion occurs most often as a late manifestation of yaws and consequently is now seen principally in the tropics It may likewise be caused by syphilis and while it is now rarely encountered in that disease there are many references in the older literature to a similar lesion Gangosa may rarely be caused by cutaneous leishmaniasis

In yaws the lesion usually begins as a gumma of the nasal septum or as a cutaneous lesion about the alae nasi Extension of the destructive process occurs over a period of months or years abetted perhaps by secondary invaders In advanced cases the entire nose is destroyed leaving a large opening directly into the nasopharynx There may be extensive ulceration of the surrounding soft parts and the floor of the nasal passages may communicate with the oral cavity because of partial destruction of the palate During the course of the active process there is commonly a foul smelling discharge Even without specific treatment some degree of healing eventually takes place Treatment for yaws will ordinarily arrest the destructive process Neoarsphenamine or mapharsen together with potassium iodide yield the best results but permanent disfigurement can rarely be prevented There is evidence which indicates that gangosa is becoming much less common in those tropical countries where yaws is being effectively treated

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RAT BITE FEVER

Definition —Rat bite fever is an acute infectious disease contracted usually from the bite of a rat and occasionally from the bites of other animals At present the etiology is in a confused state because as Brown and Nunemaker point out two apparently different micro-organisms *Spirillum minus* and *Streptobacillus moniliformis* have been considered individually responsible for the same clinical picture in man This confusion makes differentiation difficult if not impossible The spirillary infection (or so

Relationship to Other Spirochetal Diseases.—There are a number of diseases which belong to the same general group as yaws. Included among this group are syphilis, which is world wide in its distribution; bejel (Hudson, 1936) which is common among the Bedouin tribes of Syria and adjacent countries, and mal del pinto, common in parts of Central and South America, and recently discovered (Blanco 1938) to be caused by a spirochete similar to the organisms of yaws and syphilis. The precise relationship of these diseases to each other has not been determined but it is significant that for many generations practitioners have found sufficient clinical and epidemiologic differences between them to warrant the universal use of distinguishing names for each disease entity. These diseases have many features in common, but the vast majority of persons with each disease present a succession of signs and symptoms which, when taken as a whole, are very characteristic. This is particularly true with regard to yaws and syphilis; the other members of the group, bejel and pinto, have been less well studied as yet. Immunologically the situation is confused. Experimental and epidemiologic data indicate that there is some reciprocal immunity between syphilis and yaws but that this is by no means complete. Syphilis apparently gives rise to a greater degree of protection against yaws than yaws does against syphilis.

The main question therefore is whether the differences between yaws and syphilis are due to variations in the environment to which the host is subjected or whether they are due to inherent differences between the causative agents. The preponderance of evidence indicates that there are biologic differences between *Treponema pallidum* and *T. pertenue* and that these differences account in large measure for the distinctive clinical features of each disease. Perhaps in the remote past *T. pertenue* and *T. pallidum* were identical but there is no good evidence to indicate that differentiation occurred within historic times. Further discussion of this interesting question will be found in the writings of Blacklock (1937), Butler (1936), Stannus (1936) and Turner (1937).

Prognosis.—The disease is rarely directly fatal except in young infants. Without treatment the disease leads to months of partial incapacity, with the possibility of relapses over a period of many years. A not inconsiderable proportion of infected persons apparently go on, after many years, to spontaneous clinical and serologic cure. The indirect mortality from the disease due to secondary infection of cutaneous ulcers or bone lesions is probably higher than commonly supposed. With early treatment the prognosis is entirely favorable.

Prophylaxis.—No methods of artificial immunization are available. In regions where yaws is prevalent the chances of infection can be reduced by avoiding minor injuries to the skin and by protecting all open wounds and abrasions from contamination by flies. Children with infectious lesions should be excluded from school until rendered noninfectious by treatment. Efforts to control insect vectors are not practicable at the present time.

Treatment.—Yaws responds to the same drugs that are used in the treatment of syphilis, although satisfactory results and even cures are obtained in yaws with less treatment than is necessary in syphilis. The initial and generalized lesions of yaws heal promptly following the administration of the arsenical drugs. Treponemes usually disappear within two to seven days after the first injection. With four to six weekly injections a large proportion of patients remain clinically well and in many, blood serologic tests become negative. The weekly dose of neoarsphenamine is, for adults, 0.6 to 0.9 Gm. and for children 0.06 Gm. per 10 pounds of body weight. The weekly dose of mapharsen for adults is 0.04 to 0.06 Gm. and for children, 4.5 mg. per 10 pounds of body weight. These drugs should always be given intravenously. Infants and small children may be given sulfarsphenamine intramuscularly 0.1 Gm. per 10 pounds of body weight.

The lesions of yaws respond more slowly to bismuth and in general the results seem to be somewhat less satisfactory with this drug than with the arsenical preparations. Bismuth subsalicylate in oil 0.04 Gm. per 25 pounds of body weight intramuscularly is among the best of the bismuth preparations. Stovarsol (acetarsone) by mouth may be used but is not recommended. Mercury

names since the basic discoveries of Schottmuller and Blake The organism is extraordinarily pleomorphic and appears to have as one stage the so called L_1 forms of Kleineberger representing the phase of pleuropneumonia like organisms *Streptobacillus moniliformis* can be isolated from blood cultures and lesions The definitive bacteriological investigation requires highly specialized technics The sera of infected individuals contain agglutinins for the *Streptobacillus*

Pathology —There have been very few recorded autopsies of cases of rat bite fever The local lesion which is a granuloma without suppuration shows necrosis of the epithelium and dense round-cell infiltration of the corium Similar round cell infiltration occurs with the dilated vessels in the lesion of the skin eruption Lesions in the organs are chiefly those associated with a long continued febrile disease

Symptoms —In uncomplicated cases the wound of the rat bite heals promptly After an incubation period of five to fourteen days (average thirteen days with occasional long incubation periods of six weeks or more) the site of the wound swells becomes purplish and painful A chancre like indurated ulcer with a black crust may occur here and on the broader parts of the body may reach a diameter of 5 to 10 cm The regional lymphatics are inflamed and the adjacent lymph nodes become enlarged and tender The development of the local lesion is accompanied by malaise and headache and a sharp rise of temperature usually with a chill After this periods of fever alternate with afebrile periods The temperature rises abruptly to 103° to 104° F remains elevated for twenty four to forty eight hours and falls rapidly to normal within about thirty six hours The intervening afebrile periods last from three to nine days This relapsing type of fever may continue for weeks or months in untreated cases gradually subsiding Within the first week of the beginning of the fever the characteristic skin rash usually appears This is a purplish maculopapular eruption on the skin of the arms legs and trunk and occasionally on the face and scalp The skin lesions do not ulcerate They fade somewhat during the afebrile periods and reappear with new patches of eruption during the paroxysms of fever In addition to these cardinal symptoms of recurrent inflammation at the site of infection relapsing type of fever, and characteristic skin eruption there are numerous other symptoms Pains in the muscles and joints headache and vertigo are common Arthritis may occur Delirium coma and an urticarial rash with puffiness of the face occur in some cases The urine may contain albumin and casts The liver is not enlarged and there is no jaundice In long continued infection the patient becomes emaciated and secondarily anemic The erythrocyte count may be decreased to 1,400 000 and the hemoglobin to 25 per cent Leukocytosis with counts of 12 000 to 20 000 is usual at the beginning of the disease In old cases lymphocytosis has been observed A slight eosinophilia may occur during the eruptive stages During remissions most of the symptoms disappear or become less conspicuous

The Wassermann reaction is usually negative when syphilis can be excluded Positive Wassermann and Kahn reactions have been reported

The untreated disease tends to come to an end in a natural cure after several months But there are reports of infections prolonged over four eight and twenty years The mortality is said to be 10 per cent This is too high an estimate Many fatalities were due to secondary pyogenic infection Death should be rare in uncomplicated cases if properly treated

Diagnosis —The history of a rat bite followed after an incubation period of about two weeks by recurrent inflammation at the place of the bite lymphangitis and lymphadenitis relapsing fever and the characteristic skin rash is strongly suggestive of rat bite fever Sometimes there is no clear history of the bite and no local lesion when the patient is seen The rash may not be conspicuous The differential diagnosis to be considered would depend upon the area in which the patient lived As a rule it would be necessary to differentiate between undulant fever tularemia relapsing fever dengue trench fever malaria and erysipelas

The definite diagnosis should be based upon demonstration of the *Spirillum* by laboratory tests These are in order of value

doku) appears to be characterized more frequently *by an indurated ulcer at the site of* inoculation remittent fever and a purplish maculopapular rash The disease caused by the streptobacillus seems to be more often associated with abscess formation arthritis *and a variable type of fever* Neoarsphenamine and other arsenicals used in sufficient and repeated doses are effective in most of the cases of the spirillary type of infection These drugs appear to be less effective or ineffective in the streptobacillary disease Judgment must be withheld however until the etiological question is clarified This article is written by one who believes that while there are several types of *rat bite disease,* with different etiology the typical rat bite fever (sodoku) is caused by *Spirillum minus*

History—Interest in this ancient disease began with a report by Wilcox of the case seen by him in Louisiana in 1839 The modern period of study dates from Miyake's monograph on Rattenbisskrankheit *in 1900 The introduction of the Japanese name of the* disease sodoku (from *so* a rat, and *doku* poison) is also attributed to Miyake The causal agent of the *disease useful diagnostic laboratory tests and an* efficient method of treatment have been discovered by Japanese investigators

In 1914 Schottmuller isolated a Streptothrix from lesions of a case diagnosed as rat bite fever This was confirmed by Blake in 1916 The work of Dawson in 1939 indicates that the organism causing this type of rat bite infection is probably *Streptobacillus moniliformis* (*Haverhillia multiformis*) This has been confirmed by the extensive investigations of Brown and Nunemaker

Incidence and Geographic Distribution—Cases have been reported from nearly every part of the world It may be anticipated that cases of the disease will be discovered in every country where rats and man live in close association Bayne Jones collected seventy five case reports from the medical publications of the United States over the period from 1840 to 1930 Brown and Nunemaker completing the collection through 1940 have added forty four cases making a grand total of 125 reported from this country The disease is not common but its actual incidence cannot be estimated

Etiology—Francis has reemphasized the fact that rat bite fever is primarily a disease of wild rats transmissible to other rats to other animals and to man by the bite There is no evidence that fleas or other insects serve as vectors and there is no record of the transmission of the disease from man to man by excreta or fomites Cases attributable to the bites of cats ferrets and weasels have been reported

The incidence of the disease in rats is not known with certainty Reports indicate that from 2 to 21 per cent of rats in different colonies may be infected

The infecting organism is carried into the wound of the bite by the teeth or by material from the rat's mouth or lips falling on the surface of the wound The *Spirillum* has not been found in the saliva of rats It may get into the mouth and on the teeth from blood from injured gums lesions in the mouth, infectious conjunctival exudate draining through the lacrimal ducts or exudate from pulmonary lesions The *Streptobacillus* is found frequently in the exudate of chronic sinusitis chronic middle ear disease and chronic pulmonary infection in rats When several persons have been bitten by an infected rat often only the first victim has contracted the disease

Rat bite fever begins as a wound infection As this wound may be infected with organisms other than *Spirillum minus* other forms of rat bite disease occur A variety of cocci, bacilli and streptothrices have been found in these conditions Severe and fatal infections usually of a pyogenic and septicemic nature have been due to these accompanying or secondary micro organisms

The spirillary cause of rat bite fever was discovered by Futaki and his associates *in* 1916 They called the organism *Spirochaeta morsus muris* It is a spiral 3 to 5 microns long approximately 0 2 micron thick with pointed ends carrying one or more flagella The body is twisted in 1 to 4 angular spirals with crests about 1 micron apart It has never been cultivated in artificial media Robertson has identified it with *Spirillum minus* which Carter discovered in the blood of a rat in 1887 Other authorities have classified *it as a treponema or a new variety* of spirochete This organism has been found in nearly all cases in which a proper search for it has been made by inoculation of mice or guinea pigs The disease has been produced in man by inoculation of material containing the *Spirillum*

The organism now called *Streptobacillus moniliformis* has appeared under a variety of

during an epidemic in Berlin This observation was confirmed by Munch who in 1874 inoculated himself with blood containing motile relapsing fever spirochetes and subsequently developed the disease also by Motschutkoffsky (16 6) who proved the infectivity of the spirochete by inoculating the blood of patients into healthy persons

In 1891 Flugge suggested that the human body louse might act as a vector and Mackie (1907) in India reached a similar conclusion This belief was later confirmed by the inoculation into monkeys of crushed lice taken from relapsing fever patients In 1904 Ross and Milne in Uganda, showed that the "tick fever" mentioned by Livingston in 1857 was caused by a spirochete which invaded the peripheral blood stream These observations were confirmed in the Congo by Dutton and Todd (1905) who reported the mechanism of infection in the tick *Ornithodorus moubata* and the hereditary transmission of the spirochetes through the egg to succeeding generations of ticks

French Sudan and (4) on many occasions during the past the disease has been imported from Europe to the United States and has caused epidemics in cities along the Atlantic Coast In 1869–71 there was a widespread American epidemic which affected New York City Philadelphia Washington D C and many other cities

The *tick borne* relapsing fevers are endemic in (1) Africa especially tropical Africa and North Africa (2) Asia including Arabia Persia India and other parts of Central Asia (3) Europe including Spain (4) North America including Canada the United States and Mexico (5) Central

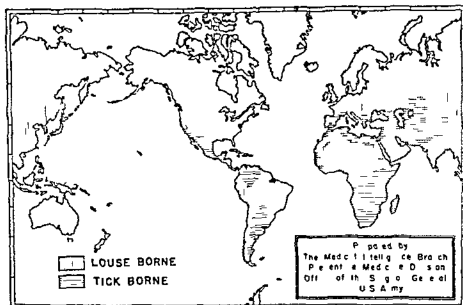


Fig 34—Geographical distribution of relapsing fever

Geographical Distribution—Relapsing fevers occur in many parts of the world as is indicated graphically in the accompanying map (Fig 34) and the distribution is influenced by various factors including the distribution of the arthropod vectors

The *louse borne* relapsing fevers have been reported as endemic in the following regions (1) Europe including the British Isles Denmark Germany Poland Russia the Balkans and Turkey (2) Asia including India China Japan Manchuria Persia and Siberia (3) Africa especially in Northern Africa including Egypt Algeria Abyssinia and Sudan and in Western Africa including the Gold Coast Nigeria Senegal and the

America and (6) South America including Colombia Venezuela Peru Uruguay and the Argentine Republic In the United States the disease has been reported in California Colorado Arizona Texas and Kansas Because of the manner of their transmission the tick borne fevers rarely become epidemic

Etiology—*The Spirochetes*—The relapsing fevers are caused by spirochetes similar to the *Spirochaeta recurrentis* discovered by Obermeier in 1868 which are demonstrable in the blood of patients *during the* febrile periods According to Bergey's Manual on Determinative Bacteriology 1940 the genus *Borrelia* Swellengrebel in

1 Inoculation of white mice and guinea-pigs with the patient s blood, exudate from the initial lesion, serum expressed from exanthematous patches material aspirated from lymph nodes or ground up pieces of tissue excised from lesions These animals are susceptible, develop infection from inoculation with very few organisms and pass through characteristic stages of the disease, with the spirilla in their blood White mice often harbor this infection spontaneously causing errors in diagnosis It is essential to ascertain by examination of the blood that these animals are free from spirilla before inoculations are made Inoculations of mice should be controlled by injections of the same suspected material into guinea pigs

2 Examination of blood and exudate from lesions by dark field illumination and stains Reports of the finding of the *Spirillum* in the blood of man are questionable It may be found in material from the lesions Wright's and Giemsa's stains are satisfactory The flagella can be demonstrated best by the use of the Tribondeau Fontana silver stain

As the organism has not been cultivated blood cultures at present offer no assistance Mistakes in examination of these cultures have been made by failure to distinguish between 'artifact spirochetes and actual organisms

Treatment —The local lesion should not be incised In 1912 Hata cured patients with rat bite fever by giving them injections of salvarsan Since then salvarsan and its derivatives have been shown to be specifically effective remedies One or two injections of the usual doses (0 1 to 0 6 Gm) of salvarsan arsphenamine neoarsphenamine, and similar compounds have brought about cure promptly Occasionally ten or more injections may be needed Other arsenical compounds bismuth and mercury have not been effective in therapy

Paresis Therapy —In 1926 Solomon and his associates recommended experimentally induced rat bite fever as a substitute for malaria in the treatment of general paralysis The infection in man has been established by the injection into the skin of the patient of 0 1 cc or less of blood from an infected guinea pig The disease thus produced is apt to be severe and may have undesirable features This form of treatment of paresis is not recommended

S Bayne Jones

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RELAPSING FEVER

(*Febris Recurrens Spirillum Fever Famine Fever Mianeh Fever Carapata Disease Tick Fever Kimputu*)

Definition —The term relapsing fever is applied to a large group of acute infectious diseases, clinically similar but etiologically distinct which are prevalent in many parts of the world These diseases are characterized by an initial febrile period lasting from three to ten days which usually begins and ends abruptly and is followed after several days of apparent recovery by one or more relapses If untreated the total course of the infection may last from six to eight weeks The relapsing fevers are caused by various closely related species of spirochetes of the genus *Borrelia* which are demonstrable in the patient s blood during the febrile attacks The infections may be divided into two large groups namely the louse borne and the tick borne relapsing fevers

History —The first known description of relapsing fever was afforded by Rutty who in 1739 reported an epidemic at Dublin The name "relapsing fever was proposed by Henderson who in 1843 described an epidemic in Edinburgh and who differentiated the disease from typhus fever In 1868 Obermeier (1873) discovered the causative spirochete in the blood of relapsing fever patients whom he studied

Palestine *O marocanus* in Spain and Morocco *O venezuelensis* and *O talaje* in Northern South America Central America and Mexico *O turicata* in Texas and Kansas and *O hermsi* in California

Available experimental data indicate that within a few days after the tick ingests infected human blood the spirochetes disappear from the digestive tract but within several days they multiply in the Malpighian tubules and other organs including the coxal glands salivary glands and legs It appears probable that the tick does not transmit the organisms through its proboscis while biting but that infection occurs by contamination of the skin puncture wound with the spirochete containing fecal fluid excreted by the tick The spirochetes are transmitted from adult female ticks through the eggs to their offspring for at least three generations Ticks of the species *O turicata* have remained infected for at least six and one half years There appears to be no specific relationship between the kind of tick and the species of spirochete

It is now believed that ticks normally become infected by feeding on infected lower animals Such animal reservoirs are probably afforded in West Africa by a shrew mouse in Panama by a wild monkey *Leontocebus geoffroyi* in Texas by armadillos and opossums and in California by squirrels and chipmunks and probably other animals

Pathology —The spirochetes may be found in the blood and the internal organs especially the spleen and the brain but the autopsy findings are not diagnostic Often the skin is jaundiced and there may be numerous small subcutaneous or submucous hemorrhages The spleen is enlarged and histologically it shows simple hyperplasia The liver is slightly enlarged Hemorrhagic meningitis has been reported It appears likely that death is rarely caused by the relapsing fever but can be attributed to complicating conditions and infections

Symptomatology —The many types of relapsing fevers described in various parts of the world naturally differ considerably in their clinical characteristics Wide variations also occur in the symptoms observed in a single epidemic Manson Bahr has described five clinical types as follows (1) A cosmopolitan type due to *S recurrentis* (2) an Iranian type due to *S persica* (3) a Central African type caused by *S Duttoni* (4) a Spanish type due to *S hispanicum* and (5) a Central and South American type produced by *S venezuelensis* Strong has discussed the symptomatology of the relapsing fevers of Africa North Africa Europe India China Persia Panama and North America

The more important characteristics of these different types may be briefly summarized as follows

The incubation period is estimated at from two to fifteen days the average being about seven days

The initial attack may last from two to seven or more days It usually starts abruptly with chilliness or a chill followed by a high fever intense headache pains in the muscles and joints nausea vomiting photophobia dizziness and sometimes epistaxis The temperature rises quickly to 104° or 105° F or higher and except for slight morning remissions it remains elevated throughout the initial febrile period at the end of which it falls to normal by crisis The pulse also rises quickly and soon reaches 110 to 140 beats per minute Periods of sweating may occur during the first day but thereafter the skin is hot and dry and the face is flushed Jaundice may occur but is more likely to appear later An erythematous rash is common during this period and later rose colored spots may occur on the trunk and limbs According to Manson Bahr the rash generally is most marked in the region around the neck spreading in a semicircular fashion from the tips of the mastoid processes thence it ranges in a symmetrical manner round the shoulders down the sides of the chest and abdomen to the inner aspects of the thighs and to the extensor and flexor aspects of the forearms The individual petechiae may be as large as a three penny bit and need to be carefully differentiated from the exanthemata of typhus and hemorrhagic smallpox Labial herpes may occur

Frequently the patient complains of severe headaches and of muscular and joint pains In case of high fever there may be delirium Insomnia may be an important symptom and hyperesthesias of the taste and tactile senses may occur It has been suggested that the spirochetes of relapsing fever

cludes six species which cause relapsing fevers in the following regions *B recurrentis* (European), *B duttonii* (West African) *B kochii* (East African) *B berbera* (North African) *B carteri* (Indian) and *B novyi* (American)

BACTERIOLOGY —Morphologically these spirochetes are indistinguishable and in general they conform to the description of *Borrelia recurrentis* This is a delicate spiral thread like organism 8 to 30 microns long and 0 3 to 0.5 micron thick, with pointed ends and from 4 to 10 large wavy irregular coils There is a spring like axial filament on which there is a layer of contractile protoplasm enveloped in a delicate periplast also fine terminal filaments but no flagellae The organism can move in either direction The spirochetes may be stained with the ordinary aniline dyes and preferably by methods commonly used for staining blood films They can be destroyed by exposure to 10 per cent saponin or to 10 per cent bile salts

Methods are available for cultivation of the organisms in artificial media Noguchi used ascitic fluid containing a piece of sterile rabbit kidney and a few drops of citrated blood, incubated at 37° C under anaerobic conditions Later workers have used semi solid media or developing chick embryo As such culture methods sometimes fail they are rarely used for routine diagnosis

Certain lower animals are susceptible to experimental infection and according to Novy and Knapp *B recurrentis* *B novyi* and *B duttonii* have been differentiated according to their infectivity for monkeys mice and rats It is claimed that rabbits and guinea pigs are relatively unsusceptible although they may be infected with *B carteri* and guinea pigs have been infected with some American strains It is of interest to note that spirochetes resembling those of relapsing fever but producing different symptoms have been found in various natural infections of lower animals and birds

In man and in animals recovery from the infection is followed by a transient immunity and the appearance in the serum of specific spirocheticidal lytic and agglutinating antibodies

Transmission —Relapsing fever can be transferred by the injection of blood containing the spirochetes into normal persons The organisms are able to penetrate the mucous membranes of the eye and possibly of other parts of the body they can also cause infection when rubbed into the apparently intact skin It appears that under natural conditions the disease is spread by blood sucking arthropods which may act either as contaminated mechanical carriers of infection or as biological vectors Fleas bedbugs lice and ticks have all been suspected as potential carriers but most of the infections appear to be spread either by lice or by ticks

LICE —Human lice (*Pediculus humanus* var *corporis* and var *capitis*) have long been accepted as vectors of *B recurrentis* (Syn *S recurrentis*), the cause of European typhus fever Manson Bahr believes that *S novyi* *S carteri* and *S berbera* are similar to *S recurrentis* and that the fevers which they cause in Europe Asia and North America are conveyed by lice Stron states that European Indian Chinese West African and some of the North African infections are transmitted by the louse *P humanus*

Lice feeding on patients during febrile periods may ingest spirochetes some of which survive the louse s gastric juice quickly enter the hemocele and are distributed throughout the entire body cavity After four to six days the organisms become abundant in the hemocele and the louse contains infective spirochetes for several weeks and possibly during the rest of its life The organisms do not pass through the egg to the louse s offspring Apparently the infection is transmitted to man not by the bite of the louse or through contamination with the feces but by crushing the infected louse on the human skin The released spirochetes may then enter the skin or contaminate the fingers and thus reach the mucous membranes of the eye

TICKS —The tick borne relapsing fevers caused by *B duttonii* and other species or varieties of spirochetes are transmitted by ticks of the family *Argasidae* especially of the genus *Ornithodorus* The following species have been suspected or shown to be vectors *O moubata* in Southeast and Central Africa *O erraticus* in Tunis *O papillipes* and *O tholozani* in Central Africa and

they may be present in the afebrile period If spirochetes are not demonstrable microscopically, specimens of blood should be injected into white rats or white mice The blood of these animals should then be examined for spirochetes daily for several days

Prognosis —The reported mortality has usually been low 2 to 6 per cent but in certain epidemics in West Africa the death rates have exceeded 50 per cent The deaths usually occur among weak poorly nourished individuals especially young children and the aged Untreated cases may last as long as six to eight weeks However the disease can be cured in a short time by treatment with neoarsphenamine or related arsenicals

Immunity —Recovery from an attack of relapsing fever confers a transient immunity at least to the same type of spirochete It also produces specific antibodies in the serum Possibly the relapses are usually less severe than the initial attack because the immunity increases with each relapse until the infection is overcome It has been reported that reinfection can occur in man as early as two months However the natives of endemic regions appear to possess considerable immunity which probably is acquired through repeated infections

Prevention —The prevention of relapsing fever naturally depends on the protection of susceptible individuals from the arthropod vectors The louse borne fevers can be prevented by taking all of the precautions necessary to avoid exposure to body or head lice These measures include the maintenance of good personal hygiene and cleanliness and the disinfestation of lousy persons and clothing

The tick borne infections are more difficult to control as these arthropods do not live on the victim but as a rule live in the floor or walls of native houses in the earth of old camp sites in cracks in the floors and walls of caves and in the burrows of various small animals Such places should not be selected as camp sites and care should be taken to avoid exposure to ticks which usually come out of their hiding places at night and feed on their hosts

According to Manson Bahr a prophylactic vaccine made of killed cultures of *S recurrentis* has been used by Russian workers and found to produce specific spirochetolysins in the serum However, attempts to protect animals with killed vaccines have failed

Treatment —The patient should be kept in bed given a liquid diet and treated both symptomatically and specifically The specific treatment usually recommended consists of a single intravenous injection of neoarsphenamine or some related arsenical compound According to Manson Bahr (1940) who prefers novarsenobillon the arsenical should be given when the temperature is on the rise and not when it is declining or during the apyrexial period If treatment is not begun during the initial attack one should wait until the first relapse and then give it as the temperature rises If given at the time of the crisis, a severe reaction may occur due to the liberation of large amounts of toxic materials from the bodies of the destroyed organisms and in certain types of infection such as the Central African relapsing fever this may on rare occasions cause a fatal collapse Albuminuria is not considered a contraindication to the use of arsenicals

Neoarsphenamine is commonly recommended for use intravenously in doses of 0 01 Gm for each kilogram of body weight A single dose usually cures but two or three doses may be required Mapharsen has been used in a few cases with good results and it is believed that this drug may eventually replace neoarsphenamine It should be used in doses of from 0 04 to 0 06 Gm intravenously

Certain observers have reported cases in which neoarsphenamine failed to cure the disease and in these various other drug have been tried including bismuth preparations gold salts and the serum of convalescent individuals The therapeutic value of these materials has not been determined When intravenous injections cannot be given stovarsol may be used by mouth in doses of six tablets (4 gr or 0 25 Gm each) daily

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are neurotropic They may persist in the brains of the experimental animals for periods of more than a year In the tick borne Central African type, *severe nervous lesions* have been noted On rare occasions, optic atrophy has occurred immediately after the fever or several months later At times hemiplegia aphasia or other nervous symptoms may occur suddenly during the disease *In such instances the spirochetes may be* demonstrable in the cerebrospinal fluid which also contains an excess of lymphocytes and is under increased pressure Cases have also been reported with symptoms resembling encephalitis and meningitis

The tongue is usually coated and moist but in severe cases it may be dry and brown Nausea and vomiting are common and they may persist even during the apyrexial period The vomitus may contain bile or it may resemble the black vomit of yellow fever Anorexia is common and the patient usually is constipated however diarrhea has been associated with severe types of the disease Abdominal pain is a common symptom and gastric or intestinal hemorrhages have been reported The liver may be enlarged and tender, and jaundice may be severe The spleen is usually large and tender

Pulmonary symptoms including a bronchial catarrh frequently occur during the initial febrile period In some epidemics pneumonia occurs in 5 per cent of the patients and is a serious complication

Urine collected during the paroxysm may contain albumin less frequently casts and rarely blood Spirochetes have been found at times in the urine and prostatic fluid

Blood collected during the febrile attack usually contains spirochetes There is a polymorphonuclear leukocytosis of 15 000 to 26 000 and the Arneth count *is deflected to* the left In about 20 per cent of cases the Wassermann test is positive during the period of infection

The period of the initial attack usually ends abruptly with profuse sweating and a rapid fall of the temperature to normal or below This may be accompanied by diarrhea In elderly or weak patients a dangerous state of collapse may occur

The first period of apyrexia which follows the crisis of the initial attack lasts from three to ten days The fever and all of the other symptoms subside The spirochetes disappear from the peripheral blood stream *The skin becomes cool and* pale the pulse falls to the normal rate and is of poor quality The prostration is great at first but in a few days, the appetite and strength return and the patient feels so well that he considers himself completely recovered

The first relapse follows this symptomless interval It is characterized by a repetition of the more important symptoms of the initial attack It may be more severe, but as a rule it is milder Jaundice is more common Conjunctivitis may occur and iritis is not rare Transient cranial nerve defects may occur and there may be uterine hemorrhages or abortion The relapse seldom lasts as long as the first attack and it also ends by crisis

Subsequent Relapses—The end of the first relapse is often coincident with convalescence but in many instances additional relapses occur Frequently, these are shorter and milder than the previous febrile periods In the louse-borne relapsing fever of Europe and Asia there are rarely more than two three or four relapses This is also true of the tick borne infections of North America The tick borne infections of Persia and Central Africa usually have four or five relapses, and the latter may have as many as eleven relapses

Convalescence may be protracted and there may be various sequelae including iritis otitis parotitis adenitis neuritis, polyarthritis nephritis and pneumonitis

Diagnosis—The relapsing fevers may be confused with various other diseases including malaria dengue yellow fever Weil s disease enteric fever typhus influenza pneumonia and early smallpox They *may be differentiated from these diseases* on the basis of clinical differences However the specific diagnosis depends on the demonstration of typical relapsing fever spirochetes in the patient s blood This is commonly done by the microscopic examination of blood as follows (1) fresh preparations examined by dark field illumination (2) thin films prepared with Wright s stain (3) thick films stained with Wright s or Giemsa s stains The spirochetes are usually found during the febrile attacks but occasionally

necrosis with distortion of the normal lobular architecture Evidence of biliary stasis in the central part of the lobule has been described and signs of regeneration of liver cells may be prominent Capillary damage is indicated by the minute hemorrhages which have been described in nearly every part of the body They are most commonly found beneath the skin peritoneum and pleura and in the intestinal tract kidneys nasopharynx, and adrenal glands The hemorrhages are usually small but may occasionally be massive The skeletal muscles show signs of active inflammation and degeneration of the individual muscle fibers The gastrocnemius muscle is most commonly involved

Spirochetes are readily demonstrable (Levaditi s stain) in the kidneys and liver and have occasionally been found in other organs The pathologic lesions described in the kidney liver capillaries and skeletal mu cles are thought to be due to a direct toxic effect of the spirochete Such clinical features of Weil s disease as jaundice azotemia myalgia and the hemorrhagic diathesis are adequately accounted for by these pathologic lesions The exact mechanism of the jaundice is not clear Hepatitis appears to be responsible for the bilirubinemia but hemolysis and biliary obstruction may be contributing factors

Other less common pathologic findings include hemorrhagic pneumonia vegetative endocarditis myocarditis and inflammatory lesions of the intestinal tract The spleen and lymph nodes are usually not enlarged

Clinical Features —The average incubation period in Weil s disease is said to be ten days but may range from four to nineteen days The clinical course of the illness may be divided into the following stages

Septicemic Stage —The first stage of Weil s disease commonly associated with spirochetemia lasts from two to five days It is characterized by sudden onset with headache chilliness myalgia and prostration There may be anorexia nausea vomiting abdominal rigidity and cough with bloody sputum On physical examination the patient appears acutely ill There is high fever (102°–106° F) and frequently a relative bradycardia The skin is hot and dry petechial hemorrhages are not uncommon and the conjunctivae are injected The throat may be moderately inflamed and signs of bronchopneumonia are sometimes described The abdomen is usually soft although there may be tenderness of the abdominal wall The muscles of the legs and back are tender and signs of meningeal irritation are common These symptoms and signs increase in severity as the disease progresses

Icteric or Toxic Stage —It is estimated that not more than 50 per cent of patients with Weil s disease become jaundiced The nonicteric form of the disease passes from the first stage directly into the third or convalescent stage In the more severe cases jaundice develops (most frequently on the fifth day) and may become very intense Pruritus is rare At about the same time there appears evidence of renal failure with oliguria and even anuria The hemorrhagic tendency also becomes apparent in the second stage of the disease and is characterized by purpuric and ecchymotic spots in the skin and petechial hemorrhages in the mucous membranes and conjunctivae The patient appears profoundly ill and may lapse into coma or become disoriented and delirious

The temperature is lower than in the first stage (98°–101° F) but the pulse increases (100–130) and respirations may be rapid Signs of patchy consolidation are occasionally encountered in the lungs and the liver is enlarged and moderately tender The spleen is seldom palpable Moderate abdominal distention is common and tendon reflexes are diminished

In fatal cases death usually occurs between the ninth and sixteenth days In the nonfatal cases the patient s condition begins to improve late in the second week the sensorium gradually clears the urinary output increases and the jaundice subsides Occasionally iridocyclitis or optic neuritis may develop as a late complication

During the second stage of the disease the blood becomes sterile but spirochetes appear in the urine Specific antibodies are demonstrable in the blood serum between the ninth and fourteenth days

Convalescent Stage —Convalescence begins most frequently at the end of the second week of the disease The jaundice and

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WEIL S DISEASE

(Spirochetal Jaundice Leptospirosis Icterohaemorrhagica Infectious Jaundice)

Definition —Weil s disease is a spirochetal infection caused by *Leptospira icterohaemorrhagiae* The disease is characterized by sudden onset with malaise prostration myalgia and fever and in many cases by the subsequent development of jaundice a hemorrhagic tendency and renal failure

History —As early as 1800 cases of jaundice complicated by hemorrhage conjunctivitis and renal failure were noted among French soldiers in Egypt An infection of apparently similar nature was described during the American Civil War In 1886 Weil published his classical description of jaundice occurring in young adults—a disease of sudden onset with severe shaking chills prostration hepatomegaly splenomegaly hemorrhagic diathesis and evidence of renal damage It is of interest to note that two of the features of the syndrome described by Weil (chills and splenomegaly) are now considered to be rarely associated with the disease which bears his name In 1916 Inada reported that Weil s disease was caused by a spirochete and two years later Noguchi classified the organism and named it *Leptospira icterohaemorrhagiae*

Incidence —Cases of Weil s disease have been encountered in at least forty six different countries The number reported from England France and Germany is well over 1000 and the infection has been common in Holland Denmark Japan Africa and South America The first case recognized in the United States was reported in 1922 and by 1941 sixty seven cases had been described in the American literature

The disease is far more common in men than in women the difference is apparently due to occupation The infection is relatively *uncommon in children and occurs most frequently* in adolescents and young adults The majority of cases occur during the summer months

Mode of Infection —*L icterohaemorrhagiae* has been demonstrated in the excreta of more than 10 per cent of adult gray rats trapped in rural and urban districts of this country It has also been recovered from dogs mice cats pigs foxes and horses The organism will survive for at least three weeks in stagnant water The commonest source of human infection is stagnant water which has been contaminated by murine excreta *The portal of entry is usually* an abrasion on the skin but may be the gastro intestinal tract the nasal mucous membrane or the conjunctiva Fish cleaners miners sewer workers tunnel diggers sugar cane cutters and workers in rice fields are the most frequent victims of the disease Each of these occupations involves work in wet places where rats are common Seventy-one cases were reported in Rotterdam among persons who had accidentally fallen into dirty canals or who had been swimming in a single infected swimming pool The infection may also be transmitted through contaminated drinking water

Pathology and Pathogenesis —Patients dying of Weil s disease are found to have prominent pathologic lesions in the kidneys liver capillaries and skeletal muscles The enlarged bile stained kidneys show swelling and necrosis of the epithelium of the convoluted tubules and interstitial infiltration of the kidney parenchyma with both lymphocytes and polymorphonuclear leukocytes Although glomerular lesions resembling those of hemorrhagic nephritis may occur the demonstrable renal damage is predominantly tubular The liver is often slightly enlarged No signs of obstruction are to be made out in the larger bile ducts and although inflammation and occlusion of the finer intrahepatic biliary ducts have been described they are thought to be uncommon Direct injury to liver cells is indicated by cloudy swelling and scattered areas of focal

failure or extensive hemorrhages The non icteric form of Weil's disease is rarely, if ever fatal

Treatment—Supportive treatment should consist of adequate salts and the administration of 3 to 5 liters of fluid a day during the febrile stage of the illness (by intravenous route if necessary) A liquid or soft diet should be prescribed high in carbohydrate and supplemented by intravenous glucose therapy if the jaundice is severe Daily enemata should be employed if necessary to combat abdominal distention Since the patient's excreta may be infected they should be sterilized before being disposed of

Arsenical drugs are relatively ineffective in the treatment of Weil's disease and their use is considered hazardous in the presence of liver and renal disease Soluble bismuth preparations (sodium bismuth tartrate) are effective in experimental leptospiral infections in guinea pigs and both soluble and colloidal bismuth compounds have been used with some success in human cases of spirochetal jaundice The most promising form of specific treatment however appears at present to be serum therapy Specific antiserum prepared in horses has been found to be effective in lessening the severity of the disease and decreasing the mortality particularly when administered early in the course of the infection Although rather extensively used in Europe specific antiserum is unfortunately not available at present for general use in this country Convalescent serum may serve as a satisfactory substitute in certain cases

Prophylaxis—Prophylactic vaccines containing killed cultures of leptospira have been employed particularly in Japan but the efficacy of vaccination as a preventive measure remains to be established Public health regulations designed to prevent workers from coming in contact with infected stagnant water are doubtless effective in lessening the prevalence of the disease

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PROTOZOAN INFECTIONS

AMEBIC DYSENTERY

(Amebiasis Entamebiasis Amebic Colitis)

Definition—Amebic dysentery is a specific infection originating in the large intestine and characterized by discharges of blood and mucus Secondary lesions may occur, especially in the liver The causative microorganism is *Entamoeba histolytica*

There are many conditions in which diarrhea or dysentery may appear as an occasional symptom but in two infections namely bacillary and amebic dysentery the cardinal manifestation is a frequent discharge of blood and mucus The bacillary type of infection is a fairly simple process but amebic dysentery has commanded the attention of workers in several fields because of its interesting etiology its striking pathology and the comparatively satisfactory methods for its diagnosis and treatment

History—Attention was first directed to amebae as the possible cause of dysentery by Lösch in 1875 but his suggestion was not received very seriously on account of the occurrence of acute cases of dysentery without any amebic infection Amebic dysentery was established as a definite entity in 1891 by the pathologic studies of Councilman and Lafleur The situation was greatly simplified about 1900 when the etiology of bacillary dysentery was fully established but there was still much confusion because of the fact that amebae were frequently found in the stools of healthy people A definite step toward the clarification of this difficulty was taken by Schaudinn in 1903 He suggested that the amebae commonly seen in the feces of man could be separated into two distinct species—a pathogenic and a nonpathogenic type The former he named *Entamoeba histolytica* on account of its ability to dissolve tissues—the harmless form he called *Entamoeba coli* The recognition of a nonpathogenic ameba in the intestinal tract of man was a fundamental step in establishing the etiologic role of *E histolytica*

Nomenclature—Protozoologists readily distinguish the genus *Entamoeba* of man from a quite distinct type *Endomoeba blattae* living in a very differ-

evidence of renal insufficiency gradually disappear and the patient becomes symptom free except for weakness Convalescence may occasionally be prolonged for eight to ten weeks because of persistent jaundice Relapses are not uncommon in the third fourth or fifth weeks but they are usually mild lasting only a few days The specific antibodies reach a high titer in the blood *in the convalescent state and persist for* many years

Laboratory Findings—The urine particularly in the second stage of the disease, contains albumin casts and bile The stools are rarely acholic Leukocytosis (10 000–50 000) is present from the onset and is accompanied by an increase in the percentage of young polymorphonuclear leukocytes Anemia may occasionally develop but the platelets and prothrombin time are normal The icterus index may exceed 300 and the van den Bergh reaction is variable The nonprotein nitrogen and blood urea nitrogen of the blood are increased in the second week of the disease and the carbon dioxide combining power of the blood is depressed in cases of severe renal insufficiency In most cases examination of the spinal fluid gives evidence of meningitis in the early stages of the disease There is a moderate increase in spinal fluid protein the Pandy reaction is positive and the cell count ranges between 50 and 1000 cells per cubic millimeter Approximately half of the cells may be polymorphonuclear leukocytes

Specific Diagnostic Methods—*L ictero haemorrhagiae* may be recovered from the blood during the first week The organism is demonstrated with only the greatest difficulty by direct examination of the blood under the dark field microscope since filaments from red blood cells often float free in the plasma and are easily mistaken for leptospira The most practical method of bacteriologic diagnosis is the inoculation of blood intraperitoneally into a young guinea pig (175 Gm or less) Within ten to fourteen days the pig will usually become jaundiced and die and the organism can be identified at autopsy The organism may occasionally be recovered before the onset of jaundice by aspirating the peritoneal cavity

The spirochete of Weil s disease appears in the urine in the second week of the disease Dark field examination of the urine is unsatisfactory but guinea pig inoculation with the sediment of freshly voided neutral urine will often result in recovery of the organism The leptospira may occasionally be demonstrated in the spinal fluid or in the sputum by the same method

Specific antibodies which appear in the blood after the tenth to the fourteenth day are measured by the agglutination test The presence of agglutinins for *L icterohaemorrhagiae* in dilution of 1 300 or above is considered diagnostic Serum containing the specific antibodies also causes lysis of the organisms A negative agglutination reaction after the thirtieth day of illness practically rules out the diagnosis of Weil s disease Several immunologically different strains of *L icterohaemorrhagiae* however, have been described and Weil s disease may rarely be caused by a canine strain of leptospira (*Leptospira canicola*)

Differential Diagnosis—Early in its course Weil s disease simulates numerous severe infections associated with bacteremia the illness being frequently confused with *typhoid fever* Mild attacks of the nonicteric form of the disease resemble influenza

In the presence of icterus leptospirosis may be mistaken for acute *catarrhal jaundice* Elevation of the leukocyte count, the absence of lymphadenopathy and splenomegaly evidence of renal disease a hemorrhagic tendency and meningeal signs all serve to distinguish the spirochetal infection

Perhaps the most difficult problem in differential diagnosis is presented by *yellow fever* Certain features however, seem to distinguish it from Weil s disease Early in the course of yellow fever the patient s face is intensely flushed there is an appearance of anxiety and the pulse is rapid As the jaundice develops the pulse becomes slower whereas the reverse is true in Weil s disease The absence of leukocytosis and a normal red blood cell count are also distinguishing features of yellow fever

Prognosis—Reported case fatality rates for Weil s disease have varied in different epidemics from 4 per cent to 48 per cent. In a series of 452 cases studied in Holland 10 2 per cent of the patients died The prognosis is poor in individuals over sixty years of age and in those with severe renal

in the small intestine a four nucleated ameba emerging from each cyst Following nuclear division such forms give rise to 8 typical trophozoites which are commonly arrested at points of stasis in the large bowel such as the cecum and ascending colon and in the sigmoid flexure and the rectum Only vague conjectures are available concerning the exact nature of the stimuli which incite en cystation and excystation

Morbid Anatomy —The primary lesions are confined to the large bowel in long standing cases ulcerated areas may be found throughout its entire extent Occasionally the lesions extend from the cecum into the appendix Rarely in advanced cases inva sion of the lowest portion of the ileum has occurred Experiments upon lower animals indicate that the ileocecal valve affords con siderable mechanical protection to the ileum against migration of amebae from the cecum Bacillary dysentery produces an acute dif fuse inflammation while in amebic dysen tery even in advanced cases islands of normal mucosa are found in the affected areas

The amebae are able to injure and pene-trate the normal mucosa and then rapidly invade the submucosa Microscopically amebae are seen in great numbers It seems probable that they often invade the blood vessels and are frequently carried to the liver but that only a small proportion are able to gain a foothold and set up hepatic lesions The lesions of the liver vary in detail Mul tiple abscesses may occur but often a soli tary abscess is found which may ultimately attain a relatively enormous size and rup ture into the peritoneal cavity or through the diaphragm into the lung *E histolytica* is the only pathogenic micro organism which is constantly present in the lesions but the invading bacteria influence the character of the contents of the abscess and modify the reaction in the surrounding tissue Lique faction of the contents may be delayed thus rendering difficult the attempt to locate an abscess by aspiration The amebae are found in the granulation tissue comprising the wall of the abscess and not in the necrotic cen ter Consequently they are not seen in the pus which is drawn off at operation but after a few days they make their appearance in the discharge from the granulating wall

Symptoms —The *incubation period* is variable and difficult to estimate As deter mined experimentally in man amebae ap-pear in the stools often within four to six days after the ingestion of cysts but the development of symptoms is very irregular Of eighteen volunteers parasitized with his tolytica only four developed dysentery, the symptoms appearing at twenty, fifty seven eighty seven and ninety five days after the infective feeding

The *onset of symptoms* may be sudden or gradual The bowel movements are accom panied by a moderate degree of tenesmus and abdominal discomfort There is usually no nausea and the appetite remains unaf fected If the patient is untreated the symp toms may subside more or less completely in a few weeks only to reappear again In deed a history of intermittent attacks of dysentery at once directs suspicion toward an amebic infection These untreated pa tients may become carriers but more com monly a chronic diarrhea develops The in vading bacteria eventually play a prominent part in the symptoms Periods of low fever and leukocytosis appear from time to time The patients become anemic and emaciated and are slowly but steadily exhausted in the course of years Fulminating cases have oc curred in which bacterial complications ap-pear to be responsible for signs of marked toxemia or even for perforation of the in testine whereas the usual course of the dis ease is slow giving ample time for the for mation of adhesions

Complications and Sequelae —With the improvement in diagnosis and treatment in vasion of the liver has become less common Abscess of the liver has been noted in car riers who have never showed any intestinal symptoms and also in patients long after the intestinal symptoms have subsided Sec ondary metastatic infection of other viscera has been observed for example the develop-ment of abscesses of the brain and spleen Armitage found reports of forty eight cases of brain abscess in the literature

Mixed infections with bacillary and amebic dysentery may occur but are not common The author has on several occasions seen amebic dysentery develop during an attack of typhoid fever

In the healing of extensive lesions of the

ent host the cockroach An International Commission appointed for the consideration of nomenclature turned to other fields and exceeded its purpose by attempting to analyze the generic classification of these amebae but without adequate reference to protozoological material or to representative literature With this limited information the Commission in violation of the International Code recommended that the genus *Entamoeba* be suppressed and the species *histolytica* and *coli* of man be transferred to the distant genus *Endamoeba* of a cold blooded host the roach This opinion has been ignored except in much of the literature from this country where the designation of *Endamoeba histolytica* is often employed Dobell has discussed the situation fully and with fairness to all concerned This textbook in all of its editions has adhered to the acceptable designations *Entamoeba histolytica* and *Entamoeba coli*

Etiology—Of the many genera and species which have been described *Entamoeba histolytica* is the only clearly established pathogenic ameba of man *E dispar* of Brumpt has not been fully accepted as a new species distinct from *E histolytica* The parasitic but nonpathogenic group includes *E coli* *Endolimax nana* *Iodamoeba butschlii* and *Dientamoeba fragilis* Cysts of nonparasitic amebae occasionally pass mechanically through the intestine without colonizing In earlier years some of these species caused confusion but it has been clearly established that they are entirely without etiologic significance These forms are easily detected by cultivation on a nutrient poor medium but not by procedures which are suitable for *Entamoebae*

By experimentation on man Walker and Sellards demonstrated that *E coli* is non pathogenic but it is parasitic and readily establishes itself in the intestine When passed in the feces it does not multiply in nature The pathogenic form *E histolytica* was fed to twenty volunteers eighteen of whom become parasitized and four of these eighteen contracted typical dysentery The fourteen remaining individuals developed no symptoms It is clear from this experiment and from subsequent observations that a considerable number of individuals become carriers of *E histolytica* without the appearance of any symptoms of dysentery These persons are conveniently designated as *contact* or perhaps better as *symptomless carriers* by way of distinction from the *convalescent carriers* who have recovered from clinical symptoms The distinction may at times be a difficult one especially if it is based only on the patient s history

As early as 1875 Losch infected lower animals with *Entamoeba histolytica* and produced a typical acute dysentery Amebic dysentery sometimes develops spontaneously in lower animals, particularly in dogs The more important features of the human disease including abscess of the liver can be reproduced in kittens Clinically and experimentally the course of an infection indicates that *E histolytica per se* does not induce toxic manifestations, in a large measure fatal results are attributable to bacterial invaders The observation of Schaudinn that *E coli* readily parasitizes young kittens remains unconfirmed

The cultivation of *E histolytica* was accomplished by Cutler but dependable methods were first introduced by Boeck and Drbohlav Extensive improvements were developed by Cleveland and Collier who recommended slants of a liver infusion agar or Loeffler's blood serum covered with a 1 to 6 dilution of horse serum in saline

Epidemiology—Amebic dysentery is usually regarded as an endemic disease of tropical and subtropical climates but it has also established itself in the colder parts of the temperate zones Under natural conditions the cases occur sporadically the mode of transmission not being favorable for the development of epidemics With the artificial aid of man explosive outbreaks have occurred such as the one which developed during the exposition of a Century of Progress at Chicago in 1933 Ordinarily the incidence of infection in a community is built up gradually and many surveys have been made to determine the percentage of carriers Thus the examination in Philadelphia of 1060 healthy college students revealed the presence of *E histolytica* in about 4 per cent

The trophozoites and the cysts of *Entamoeba histolytica* are excreted in the feces but no multiplication takes place outside of the host The trophozoites degenerate rapidly and if ingested by man they are easily destroyed by the digestive fluids The cysts are much more resistant and are the means of transfer of the infection from person to person On being ingested with drinking water or with food they readily set up infections either with or without the appearance of symptoms Excystation occurs

crons) than either of the two entamoebae just described and the nucleus contains a mass of chromatin arranged in a large eccentric karyosome The typical cyst is ellipsoidal in form and contains four nuclei The morphologic details are brought out clearly and beautifully in preparations stained with Heidenhain's hematoxylin Cultures are valuable as an accessory aid in diagnosis Under ordinary circumstances it is quite unnecessary to subject the patient to the discomfort and inconvenience of proctoscopic examination either for diagnosis or for the purpose of following the effects of treatment

Prognosis —A patient developing an acute dysentery is in the main fortunate if the diagnosis of amebiasis is established Under early and adequate treatment the outlook for complete recovery is very good In neglected cases of many years duration accompanied by secondary bacterial infection there may be little hope for restoration to full health

Prophylaxis —There is no method of specific protection against amebic infection Personal measures depend upon the usual hygienic precautions

Treatment —The patient need be at rest in bed only during the stage of acute symptoms The *diet* should be bland but the amount may be liberal Drugs are available in considerable variety for specific treatment

Emetine and Its Derivatives —For specific treatment compounds of emetine have been prepared for oral use and for intramuscular injection Emetine bismuth iodide contains about 30 per cent of emetine and it is almost insoluble in neutral or acid solution but dissolves readily in the alkaline contents of the duodenum Three grains (0.2 Gm) contained in an *ordinary* gelatin capsule are given by mouth at bedtime for twelve consecutive nights Notwithstanding its extremely slight solubility in the gastric contents some nausea and even vomiting may follow its administration If necessary tincture of opium may be used to control the nausea Emetine hydrochloride by intramuscular injection is the treatment of choice when lesions of the liver have developed The customary dosage is 1.5 grains (0 1 Gm) daily for a period of twelve days The blood pressure should be taken before the administration of emetine is commenced The earlier signs of toxic action consist in a fall of blood pressure and irregularity in cardiac action Diarrhea may develop as a puzzling complication the appearance of peripheral neuritis is a serious sign The margin between the toxic and the therapeutic dose of emetine is small It is excreted or detoxified with extreme slowness and tends rather to become fixed in the tissues A rest period not of several weeks but preferably of several months is demanded theoretically before repeating a course of treatment Infection with amebae as well as treatment with emetine may produce serious symptoms and the exigencies of a situation may require proportionately larger doses with repetition after a rest period of perhaps only a few weeks

Carbarsone has established itself as the chemotherapy of choice for amebic infection of the intestine Emetine may be used for refractory cases of amebic dysentery for the patient for whom arsenicals are contraindicated and for the treatment of amebic hepatitis

Arsenicals —Carbaminophenylar onic acid (carbarsone) was introduced clinically by Reed and his associates The administration is simple for adults 4 grains (0 25 Gm) is given twice daily by mouth for ten days Toxic manifestations appear to be rare and relapses less frequent than after emetine The proportion of relapses is inevitably higher in neglected patients who have received no treatment until after the infection is thoroughly established It is desirable to avoid the use of arsenicals in patients showing impaired function of the liver or kidney

The clinical results obtained by the use of emetine or carbarsone are often striking However these drugs do not lend themselves in a reliable manner as a therapeutic test for the diagnosis of dysenteries of doubtful etiology

Castela nicholsoni contains an active principle probably a glucoside which is of distinct value in the treatment of amebic dysentery Unfortunately reliable preparations of this plant are not available commercially

The *halogenated oxyquinolines* (chiniofon and vioform) have enjoyed some measure of success but they have not yet established themselves in routine practice

intestine the excessive formation of scar tissue sometimes leads to partial obstruction A child of fourteen years with a giant colon, who was thought for a time to have Hirschsprung s disease, proved ultimately to have an amebic infection of about nine years' standing

Immunity—An acute attack of amebic dysentery affords no protection against subsequent infection Relapses are the rule in an infection of the intestine whereas an amebic lesion of the liver when once healed shows no tendency to recur Encystment of *E histolytica* does not take place in the liver or other tissues

Diagnosis—The history of the patient may be helpful At the onset of an amebic infection the dysentery is often intermittent in character in contrast to the continuous symptoms usually seen in the bacillary types and in chronic ulcerative colitis Eventually in the amebic cases the remissions tend to become less marked Physical examination of a patient with moderate symptoms reveals little except abdominal spasm and tenderness over the affected portions of the bowel The temperature and the pulse rate may be normal or slightly elevated

The possibility of involvement of the liver must be remembered An abscess high in the dome may produce few physical signs An advanced lesion may lead to weakness and anorexia, the development of fever and leukocytosis accompanied sometimes by chills and sweating X ray plates seldom reveal an abscess but fluoroscopy sometimes shows limitations of motion of the diaphragm Exploratory aspiration is commonly practiced The presence of pleural pain with some dulness on percussion and the successful aspiration of pus have led to the erroneous diagnosis of an empyema

The symptoms produced by *E histolytica* a highly organized protozoon are imitated rather closely by the simple bacillary infections In the acute stage the chief difference is seen in the toxemia characteristic of the Shiga type of bacillary dysentery In the differential diagnosis one must take into consideration the intestinal symptoms which arise in diseases such as schistosomiasis tuberculosis carcinoma and even syphilis of the rectum Erroneous diagnoses in various parts of the country were a serious factor in the case of some of the patients whose infection originated in Chicago

Microscopic Examination—In the differentiation of bacillary and amebic dysentery the general character of the stools should be noted In acute bacillary infections the fluid stools contain but little fecal matter a moderate amount of mucus and often considerable blood which may be partially laked Microscopically many pus cells are seen together with large and small mononuclear cells The nuclei of these cells are rich in chromatin and may be seen in the unstained smears in contrast to the small chromatin poor nucleus of *E histolytica* In amebic cases the stools usually contain considerable fecal matter mixed with blood and mucus and the cellular exudate is less abundant In countries where bacillary dysentery of the Shiga type is prevalent a prompt provisional diagnosis permits early treatment with serum without waiting for the completion of the bacteriologic examinations

The rapid degeneration of the motile forms of entamoebae in stool specimens require entirely fresh material for examination The distinction between *E histolytica* and *E coli* concerns the field of protozoology The motile forms measure approximately 20 to 30 microns and they are not strikingly different in their appearance The nucleus of each is small in proportion to the size of the cell and very poor in chromatin *E histolytica* presents evidence of greater motility The ectosarc is clear and hyaline phagocytosis is active the amebae often being filled with red cells but seldom with bacteria *E coli* is usually sluggishly motile and freely ingests bacteria but seldom contains red cells since ordinarily none are available There is on record 1 authentic instance in which *E coli* in the presence of a bleeding papilloma of the sigmoid ingested red cells in moderate numbers In typical cases the differentiation of the trophozoites of the two species is easy in borderline cases it may be very difficult The cysts of *E coli* are fairly large (approximately 15 microns in diameter) and typically contain eight nuclei The cysts of *E histolytica* vary in size (7 to 15 microns) and typical forms contain four nuclei Super and subnucleated forms of both species occur *Endolimax nana* in its vegetative stage is smaller (10 mi

of malaria is low and is largely limited to the southeastern states and the Mississippi River basin there are nearly 1 000 000 cases with 5000 deaths

Etiology —The specific etiologic agent of malaria is a unicellular organism which lives at the expense of the red blood corpuscles in certain reptiles birds and mammals and belongs to the order of *Hemosporidia* class *Sporozoa* and the single genus *Plasmodium* The species within the genus are not numerous and they are capable of producing infections only in hosts that are closely related In man malaria is produced by four specific parasites known as *Plasmodium vivax P malariae P falciparum* and *P ovale* There are certain similarities but each has distinct morphology and definite pathogenicity and none of them has been found to be infectious for any of the lower animals Unlike virus or bacterial diseases the etiologic agent of malaria has not been successfully cultivated on an artificial medium nor in the presence of living cells outside its respective host The only means of transmission in nature is by anopheline mosquitoes although different species act as vectors in different parts of the world The anopheline mosquito does not act as a mere mechanical transmitter of the pathogen from man to man but serves as a haven where the parasite undergoes a definite development necessary for the perpetuation of the organism An artificial method of transmission is the hypodermic syringe commonly used by drug addicts which results in the actual transfer of infected blood from a carrier to a susceptible person This type which occurs more often in the larger cities is responsible for many deaths as it is usually the highly virulent falciparum malaria Less frequently malaria is acquired in nonendemic areas following transfusions from an infected donor There are many authenticated reports of this occurrence where children have become infected from parent donors who last had symptoms twenty or more years previously It is interesting to note that in practically all such instances the causative agent has been *P malariae*

The Mosquito Host—Many different species of anopheline mosquitoes have been described from various parts of the world Although most of them can transmit malaria they vary enormously in their susceptibility In North America *Anopheles quadrimaculatus* has been shown to be the only important vector The habitat of this mosquito extends to the southern border of Canada but the severe winters in addition to agricultural drainage and clearing have largely limited its activity as a disease carrier to the southern states The adult anopheline mosquito is identified by its spotted wings and its habit of resting at an angle Only the female mosquito can become infected as she requires a blood meal to produce fertile eggs The male is not bloodsucking Anopheline mosquitoes lay their eggs in swamps ponds and streams and the larvae lie and feed horizontally on the surface of the water a characteristic which makes them more liable to destruction by floating larvicides particularly oils and Paris green The common pest mosquito Culex lays its eggs in caves tin cans cisterns or any container of water in and about houses The larvae hang head downward with an air siphon sticking above the surface of the water and the body of the adult is parallel to the surface of its resting place It is not concerned with the transmission of malaria and is definitely a domestic mosquito while the anopheline prefers a wilder environment

Development of the Malaria Parasite in the Mosquito—In order to become infected a female mosquito must first bite a person that has male and female malaria parasites in the circulating blood as the asexual parasites cannot survive in the mosquito s stomach The sexual forms known as gametocytes initiate the cycle of development within the stomach of the mosquito where they undergo fertilization This is accomplished by the male parasite pushing out several flagella which break loose and come into contact with the female form Many attempt to penetrate but when one succeeds the foiled ones depart for other quarry (This also can be observed readily under the dark field microscope) The fertilized forms then push their way out between the stomach cells and form cysts on its outer wall These cysts known as oocysts gradually enlarge so that by the eighth or tenth day they are mature and measure about 75 microns in diameter If examined under the microscope the oocysts will be seen to be

Craig states that emetine hydrochloride should not be employed as a curative drug in amebic dysentery, but should be used only for the control of severe diarrhea or dysentery in patients presenting these symptoms After this a course of carbarsone, chiniofon or some of the other amebacidal drugs should be instituted

Relapses —The patient must be observed carefully for the appearance of recidives After apparently successful or even brilliant results amebae may be found in the feces within the first week after the cessation of treatment

The question of surgical intervention inevitably arises when neglected cases with extensive secondary infection fail to respond to medical treatment The most satisfactory type of operation is an ileostomy or colostomy without using any subsequent irrigation thus permitting the large bowel entire rest

Liver Abscess —Of the many drugs recommended for amebiasis, only emetine is suitable for treating metastatic infections of the liver and early lesions may heal promptly under its use Such a result is gratifying but there is opportunity for radical improvement in the chemotherapy of this complication When a definite abscess has formed it is altogether desirable to depend on aspiration avoiding if possible any open operation In cases where suitable drainage can be obtained only by radical surgery a mortality of 30 per cent or more may be expected

A W Sellards

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MALARIA

Definition —Malaria is an infectious febrile disease produced by several species of protozoa belonging to the single genus *Plasmodium* It is transmitted naturally from host to host only by the bite of an infected anopheline mosquito In the mosquito the development of the parasite is observed on the stomach wall and in the salivary glands while in man it is continued in the red blood corpuscles Clinically the disease is characterized by paroxysms of severe chills fever and sweating These paroxysms may occur daily (quotidian), on alternate days (tertian) or with an interval of three days between chills (quartan) After recovery from the acute attack the disease has a tendency to become chronic with occasional relapses

History —Historically malaria is an ancient disease as some of the earliest records of man show that it was recognized as a definite clinical entity In the fifth century B C Hippocrates differentiated the fever into quotidian tertian and quartan types Little or no light was thrown on the disease from that time until 1880 when a French army surgeon by the name of Laveran recognized the pigmented parasites in the red cells of a soldier in Algiers and was convinced that they were the cause of malaria Soon all the different asexual stages of the parasites were recognized in the red cells In 1897 MacCallum saw the fertilization of a female gametocyte following the exflagellation of a male parasite and correctly assumed that the malaria parasite had a sexual and an asexual cycle The incrimination of the mosquito as the vector for malaria followed the work of Theobald Smith who was the first to discover the arthropod transmission of disease when the tick was shown to be the essential intermediate host in Texas cattle fever English and Italian workers quickly applied the same principle to malaria and found certain anopheline mosquitoes were infected and responsible for the transmission in man By 1900 the details of the cycle in man and mosquito were known and the highly specialized manner by which this disease propagates itself was understood This complete information in addition to the long known efficacy of quinine as a treatment, led many to believe that malaria would soon be eradicated, but forty years later this belief remains far from realization

Malaria at the present time is one of humanity s chief scourges and there are many fertile areas that remain uninhabitable because of its influence It is probable that the combined number of deaths in all parts of the world where malaria exists amount to almost 2 000 000 annually In India the figures of the annual malaria survey show that there are approximately 100 000 000 cases with 1 000 000 deaths Even in the United States where the endemic prevalence

attack young and old red cells indiscriminately

Plasmodium ovale first described in 1923 by Stephens and now generally accepted as a definite species derived its name from the fact that the infected red cell always assumes an oval shape Otherwise its morphology and behavior are practically identical with those of *P vivax*

Morbid Anatomy —Tertian and quartan malaria rarely come to autopsy except as a contributory cause of death The pathologic lesions in these instances are in the main due to the disintegration of parasitized red cells and the accumulation of pigment In the spleen one finds the maximum evidence of an active or latent malaria infection and because of the collection of pigment no other disease presents a more pronounced pathognomonic picture either macroscopically or microscopically The spleen is usually markedly enlarged slate gray in color and of soft consistency during the acute disease The capsule is smooth tense and may even rupture spontaneously The cut surface exudes a brownish pulp and the malpighian bodies stand out Microscopically the sinuses are distended with parasitized and normal red cells The macrophages are laden with parasitic debris which is mostly pigment

The liver is usually somewhat enlarged and slightly darker than normal The microscopic picture shows the Kupffer cells engorged with parasites in various stages of disintegration There is little or no evidence of toxic degeneration in the parenchymal cells The heart lungs, kidneys and pancreas have a normal cellular structure and the only finding of interest is again the presence of pigment in the active macrophages

Falciparum malaria is responsible for the major portion of deaths due to uncomplicated malaria and likewise presents some pathologic lesions not present in vivax or quartan malaria Fatal cases are usually associated with an overwhelming infection and cerebral involvement The brain shows a gross brownish discoloration of the gray matter with macroscopic punctate hemorrhages in the white matter Stained sections reveal the capillaries filled with parasites in various stages of development The cerebral capillary occlusion shown in Fig 35 which is characteristic of falciparum malaria may also frequently be quite generalized and present a pathologic picture of congestion A pathologist is frequently able to make the correct diagnosis of this disease from a glance at the exposed tissues because of the slate gray tinge due to capillary engorgement with pigmented parasites

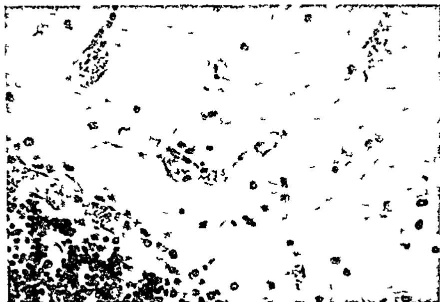


Fig 35 —Malarial parasites occluding cerebral capillaries in falciparum malaria. × 600 (Courtesy of Dr Milton Helpern Bellevue Hospital New York Photograph by J B Haulenbeck)

distended with spindle shaped sporozoites At this time they rupture into the body cavity of the mosquito and the liberated sporozoites make their way to the salivary glands where they lie and await an opportunity to enter the blood stream of a susceptible individual The sporozoites escape from the salivary glands as the infected mosquito bites an individual thus initiating the cycle of development in the human host At this step there is a missing link in the life history of the malaria parasite it was last seen as a spindle shaped sporozoite in the salivary gland of the mosquito and next observed about ten days later as a ring shaped' parasite in the human red blood corpuscle No one has recognized an intermediary form or understood the exact manner in which it attacks the red cells

Malaria Parasites in Man—The most common variety is *Plasmodium vivax* About ten days after an infection has been acquired through the bite of an infected anopheline the first parasites are observed in the red cells as circles of cytoplasm with a mass of red chromatin This stage is commonly referred to as the ring form' There follows a progressive growth of the parasite into an ameboid stage characterized by irregular arrangement of the cytoplasm appearance of pigment granules and enlargement of the chromatin The infected red cell becomes somewhat larger and paler than normal and contains numerous reddish granules known as Schuffner s dots which occur only with this species of parasite As the parasite continues to enlarge the amount of pigment increases and the nucleus starts to divide At the end of forty eight hours the red cell is a mere membrane all hemoglobin has been devoured or replaced by the parasite The nuclear fragments have assumed a rosette form with each unit known as a merozoite which is a daughter parasite As the red cell ruptures the cluster of merozoites usually sixteen in number are released and each attaches itself to a new red cell The cycle is then repeated every forty eight hours but fortunately for man not every merozoite that is released finds its way unhindered to reproduce its full quota of progeny since fully 90 per cent are destroyed by the macrophages located chiefly in spleen liver and bone marrow

For some unknown reason there is a tendency for the vivax merozoite to prefer a reticulocyte to a mature red cell for initiating its development The asexual reproduction of the parasite continues for several days when new forms appear and they are the sexual ones (gametocytes) They fill the entire red cell Their pigment is scattered and chromatin is diffuse The male parasite may be differentiated from the female by its very pale staining cytoplasm with Giemsa or other Romanowsky stains The gametocytes are concerned only with infection in the mosquito have no clinical importance and usually persist in the blood in limited numbers for two or three weeks The characteristics which differentiate *P vivax* from other parasites are a forty eight hour cycle sixteen merozoites in the mature parasite at time of segmentation, and an enlarged pale, parasitized red blood cell usually stippled with red staining granules

Plasmodium malariae which produces quartan malaria in man requires seventy two hours to complete each asexual cycle in the red cell Except for its slower metabolic activity this parasite bears a close similarity to the behavior of *P vivax* Morphologically the young parasite is frequently observed as a band form across the red cell The parasitized red cell seems to have a greater concentration of hemoglobin and is somewhat reduced in size There are usually only eight merozoites in the mature parasite and after segmentation they prefer to attach themselves to mature red cells rather than the younger reticulocytes

The asexual cycle of *Plasmodium falciparum* is first recognized as an extremely small signet ring in the red cell approximately one half the size of a *P vivax* ring Only in the severest cases are the more mature stages of the parasite seen in the red cell The reason for this seems to be that early in the acute infection there is a tendency for the ring forms to aggregate in the capillaries throughout the body where they undergo their usual development The required time for one cycle is not definitely known but is probably between twenty four and forty eight hours The gametocytes are crescent shaped a definite diagnostic finding as no other known malaria parasite has this morphology The parasite seems to

period which may vary from eighteen to forty days The onset is similar to that of vivax malaria being initiated by a low grade remittent fever lasting from three to five days and without chills The paroxysms usually occur every seventy two hours the time required for the complete development of the asexual cycle in the blood However counting from the beginning of the day of one chill to the end of the day of the next four days are required (Fig 37) which accounts for the unfortunate name quartan malaria A double quartan infection gives a chill on two consecutive days with an intervening day of normal temperature Rarely *does one encounter daily chills with quartan* malaria When compared to vivax malaria the paroxysm lasts longer is slightly more severe and the patient feels less like getting up between chills

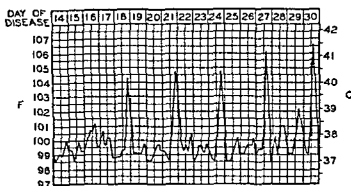


Fig 37—Temperature chart of a patient with quartan malaria

Falciparum Malaria—Falciparum or estivo autumnal malaria is a more severe disease than the others and as such is responsible for the origin of the purely descriptive terms of the disease as cerebral algid hemorrhagic pernicious and many others The latter refer to symptoms which depend largely upon the localization of the parasites The incubation period is commonly twelve days the fever is irregular and not characteristic The paroxysms are similar to those accompanying other malarias although of longer duration and occurring at more irregular intervals The temperature is usually high If there is a cerebral localization of the parasites the onset is rapid with delirium or coma and death frequently ensues without a return to consciousness The disease may present a gastro intestinal syndrome with abdominal cramps diarrhea vomiting and only a few parasites in the blood The patient is markedly dehydrated and may have a high or low grade fever Stools may contain blood resulting from intestinal capillary thrombosis and ulceration

Hemoglobinuria is frequently associated with falciparum malaria where the hemolysis of red cells is the prominent feature of the disease The urine may be tinged with hemoglobin or it may be almost black with a heavy amorphous precipitate The chills are severe the patient exceedingly ill and parasites are usually infrequent or absent from the blood stream In fatal cases the urine becomes scanty and finally is suppressed entirely

Diagnosis—An absolute diagnosis of malaria depends upon the recognition of the parasite in stained thin or thick blood smears Ordinary thin smears should be made on slides that have been thoroughly cleaned to insure even spacing of the red cells They can be stained with Giemsa s Wright s or Hastings stain For the uninitiated the thin smear method is preferred because there is less opportunity to be confused by artifacts It is easy to overlook parasites by this method however although they may be present in sufficient numbers to produce clinical activity The thick smear method is advantageous because it affords a means of concentrating the blood The thick film should be about the size of a dime on a very clean slide The two preferred methods of staining are with Giemsa s or Field s The former is satisfactory and is accomplished by adding one drop of Giemsa to 1 cc of

Symptoms—The symptoms of malaria vary according to the type of parasite producing the disease as each of the four parasites has a characteristic behavior and time of sporulation which give rise to different clinical pictures Symptoms also vary according to host resistance or immunity For example in areas of high malaria endemicity people may go about their work with no apparent difficulty and have at the same time a considerable number of circulating parasites in their blood stream Less intense infections gauged by the number of circulating parasites will completely prostrate a nonimmune individual coming into the same area There is evidence to show that strains of the same species of parasite may also have different virulence However the initial infections in susceptible individuals have certain classic features according to the species involved

Vivax or Tertian Malaria—This is by far the most common the mildest and most likely to recur Because large numbers of individuals have received the beneficial effects of vivax malaria acting antagonistically against general paresis of the insane excellent opportunities have been afforded for observing the symptoms in great detail The most thoroughly studied malaria infections were induced by the bite of infected mosquitoes and once established they were allowed to run their full course in order to obtain greatest therapeutic results On about the sixth day after the bite of the mosquito the patient has a mild backache muscle soreness and a low grade prodromal temperature without chills Paroxysms appear on about the fourteenth day Usually these paroxysms occur on alternate days and coincide with the segmentation of the mature parasite although they may occur daily (quotidian), which means that there are two broods of the same parasite, one segmenting on even days and the other on odd days of the disease or the two types may occur during the course of the one infection as shown in Fig 36 A typical paroxysm for vivax malaria consists of a cold hot and sweating" stage

Cold Stage—The patient has a chilly sensation over the entire body which gradually increases in intensity the teeth chatter the skin becomes blue and cold and there is an uncontrollable shaking In spite of heat pads and blankets it is impossible to keep the patient warm The pulse is rapid and weak and occasionally there is nausea and vomiting The cold stage lasts on the average of one hour and it subsides as the body temperature rises

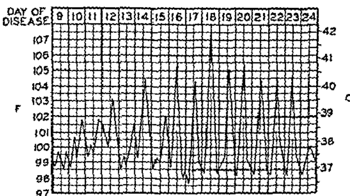


Fig 36—Temperature chart of a patient with vivax malaria showing both tertian and quotidian types of fever (Photograph by J B Haulenbeck)

Hot Stage—In this stage the patient has a flushed face severe headache and may be partially delirious with a temperature often as high as 107° F There is a sensation of intense heat with a hot dry skin and this portion of the paroxysm lasts about two hours

Sweating Stage—The sweating stage is ushered in with an abrupt onset and the patient breaks out into a profuse perspiration Temperature drops to normal the headache disappears and a feeling of well being comes over the patient Although somewhat drowsy and weak he feels able to resume work

Quartan Malaria—This parasite produces an infection after a prolonged incubation

to demonstrate specific protective and complement fixing antibodies and agglutinins in the serum of experimental animals after recovery from the acute attack The chief defense of the body against an acute malaria infection or recovery from a relapse probably depends upon a greatly accelerated rate of phagocytosis by the individual macrophages of the reticulo endothelial system

Prophylaxis —It is particularly advisable to give soldiers prisoners laborers or similar groups of personnel quinine or atabrine as a prophylactic drug where malaria is heavily endemic and where the predominant type is falciparum malaria There is as yet no known drug that will prevent the occurrence of malaria infection although both quinine and atabrine will usually prevent the development of clinical malaria as long as either drug is administered As far as their effectiveness is concerned they are comparable The prophylactic dosage of quinine is 0.3 Gm (5 grains) per day given as long as the subject resides in the infected area although some advise as much as 0.5 Gm (7 grains) The dosage of prophylactic atabrine is 0 1 Gm (1½ grains) given on alternate days

Treatment —The accepted treatment for malaria is the administration of certain chemotherapeutic drugs Specific antiserum from animals or serum from convalescent humans has not proved beneficial in the prevention or treatment of the disease Although the assertion is repeatedly made that malaria is a disease for which there are specific therapeutic drugs and that it is a simple matter to overcome the infection the fact remains that malaria is a most difficult disease to eradicate completely This is evidenced by the frequent relapses which occur after therapeutic measures considered adequate in patients who have had no opportunity to become reinfected

For many years the standard treatment of malaria has consisted of 3 Gm (45 grains) of quinine daily for one week and then 0 6 Gm (10 grains) daily for eight weeks This routine has been discarded by many because of the difficulty of inducing the patient to continue treatment for two months and because no assurance of cure could be offered Knowledge that relapses occur in spite of therapy but that they are almost always less severe and more responsive to treatment than the initial attack has brought about a new concept in malaria therapy Now the rationale is not to attempt the difficult task of eradication of the infection in one step but to bring the acute attack under control and be prepared for and treat the relapses as they occur

In addition to modification of quinine administration for malaria recent advances in therapy have been made with atabrine and plasmoquin two synthetic drugs effective against the malaria parasite Therefore at the present time there are three accepted antimalarial drugs which may be used or substituted in certain instances because of their selective action In order to determine as nearly as possible the best treatment for the individual with malaria the Malaria Commission of the League of Nations in 1937 arranged for outstanding malariologists to conduct experiments arranged beforehand on the prophylaxis and chemotherapy of malaria involving over 12 000 individuals throughout various parts of the world Their conclusions and recommendations are in agreement with those of others actively interested in the subject In general the results showed that in ordinary cases of vivax or quartan malaria it is immaterial whether quinine or atabrine is employed for the treatment of the acute attack Atabrine seems to have a distinct advantage in falciparum malaria Plasmoquin has the tendency when given with quinine or after atabrine to reduce the number of relapses which usually follow vivax or quartan malaria and is effective against the gametocytes of all three infections especially those in falciparum malaria The most successful therapeutic results will come from the proper choice of drug and with any infection it is imperative that the physician be in a position to diagnose and follow the treatment with the aid of a microscope As there is a choice the indication contraindications and method of administration for each drug are discussed separately

Quinine—The oral administration of quinine salts is advised whenever possible and should be given parenterally only when the patient is in coma or vomiting profusely Because of the shortage of quinine and because of the more rapid effect of quinine on falciparum malaria it is beneficial to give

distilled water and staining for thirty minutes *Field s method* has been recently discovered and possesses many advantages, long drying of the film is unnecessary, the entire staining takes less than ten (10) seconds and there are fewer artifacts (Consult J W Field *Trans Roy Soc Trop Med* 35 35 1941) The greatest number of parasites appear in the blood stream immediately after the chill and for the following six hours The inability to find parasites in blood films does not rule out malaria, particularly in subsiding or chronic infection Splenic puncture for diagnostic purposes is unwarranted and dangerous as it may lead to the rupture of an enlarged tense spleen The chief complaint of the patient is usually a severe chill, high fever and sweating In the history there also is usually information showing that malaria is endemic where the patient resides or that he has traveled in infected areas for example, campers and hunters frequently acquire malaria in this manner

There are few physical signs The patient appears anemic the degree varying according to the duration and severity of the disease The spleen if sufficiently enlarged to be palpated is soft in the acute disease and firm in chronic cases

There is a therapeutic diagnostic test of giving quinine to a suspect having negative blood smears and elevated temperature which is very useful if correctly interpreted It is strong evidence if the drug fails to reduce the fever that the cause is not malaria Likewise it is extremely important that the physician ascertain whether the patient has taken some remedy on his own initiative before seeking medical aid This self medication is a common practice and accounts for a temporary cessation of symptoms and disappearance of parasites from the blood stream

In addition to the diagnosis of the individual the physician is frequently called upon to determine the prevalence of incidence of malaria in a community The established routine is to obtain the parasite rate by blood smear examination from as many individuals as feasible At the same time a determination of the number of enlarged spleens and the degree of splenomegaly furnishes additional information Personal history about malaria infections in previous years is also included Such a survey will give data necessary to express quantitatively the amount of malaria in a community and if continued will furnish a guide to yearly endemicity of the disease

Prognosis—Patients with vivax or quartan malaria rarely, if ever succumb unless complicated with other diseases malnutrition, or exposure Even in endemic areas where many infections are self treated deaths are few Also in paretics where malaria has been induced for therapeutic purposes and allowed to run a full course without intervention, the death rate is almost nil Vivax and quartan malaria are diseases of high morbidity and low mortality

Falciparum malaria is the cause of practically all deaths due to malaria but if recognized early usually lends itself to therapy A guarded prognosis must be held for patient with the cerebral type in coma or stupor Malaria and hemoglobinuria always present a grave prognosis

Relapses are to be expected with all types of malaria These may occur at any time but are most likely to occur after exposure change of climate hemorrhage, or when body resistance is lowered from any cause

Immunity—A malaria infection confers a low grade but specific immunity upon its host after the acute attack has subsided This acquired immunity in man is of short duration as an individual may have repeated attacks produced by the same organism within a relatively short space of time In experimental animals the residual immunity following complete eradication of the infection persists only a few weeks It is held by many that a host is immune to malaria only in the presence of infection There is no cross immunity in human malaria as it is frequently observed that a person may have a simultaneous infection with two or more types of malaria It is highly probable that an individual is resistant only to the malaria in his particular locality for example it has been shown that a person immune to a strain of vivax malaria in Florida behaves as a normal when exposed to infection from a vivax parasite from Cuba

The mechanism of immunity in malaria is not clearly understood but it is possible

is to be avoided at all costs because it removes the body's chief organ of defense

L T COGGESHALL

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TRYPANOSOMIASIS

AFRICAN TRYPANOSOMIASIS

(*Sleeping Sickness*)

MOST investigators recognize two distinct varieties of trypanosomiasis in Africa—Gambian and Rhodesian sleeping sickness—although recently some feel that the causative agent of both may be physiologic variants of the same trypanosome Both are limited to tropical Africa The Gambian type is irregularly distributed over an enormous area and because of the habits of its insect vector *Glossina palpalis* follows water courses It is found on the west coast from Senegal southward to Angola and extends eastward from Bahr el Ghazal Lake Albert and Lake Victoria on the north to Lake Banguelo in the south The Rhodesian type is limited to a much smaller area occurring only in portions of Nyasaland Rhodesia Tanganyika Territory and Portuguese East Africa

Gambian Sleeping Sickness —The Gambian disease is caused by *Trypanosoma gambiense* For a description of this parasite as well as of trypanosomes in general the reader is referred to standard works on protozoology Suffice it to say here that *Trypanosoma gambiense* is a typical polymorphic mammalian trypanosome which varies in length from 10 to 39 microns and possesses a spindle-shaped body which moves sinuously because of its undulating membrane and free flagellum It reproduces by longitudinal fission and so far as is definitely known retains its trypaniform structure throughout its life cycle in man Transmission from man to man is effected by the tsetse fly *Glossina palpalis* After the fly has become infected by ingesting blood from an infected human being the parasites undergo a definite developmental cycle which lasts twenty days or more Eventually they invade the salivary glands where once established they constitute a constant source of infection when the fly bites uninfected persons Occasionally transmission may take place mechanically by means of *Glossina* or other biting insects or by coitus

In man the trypanosomes are found chiefly in the blood vessels and lymphatics They may however invade the connective tissue and the parenchyma of the various organs a fact which may, indeed account for the tissue lesions

The length of the incubation period has not been accurately ascertained but is probably much shorter than was originally supposed Initial symptoms have appeared in some cases fourteen days after inoculation The disease itself generally passes through two stages the first being sometimes known as the *trypanosome fever stage* and the second as the *sleeping sickness stage* The first is characterized principally by irregular attacks of fever chronic polyadenitis exanthemata frequency of the pulse and respiration and asthenia the second by exaggeration of the symptoms of the first stage marked emaciation and by the appearance of nervous symptoms tremors incoordination of movements paralyses mental disturbances apathy somnolence coma and death These two stages are as a rule not clearly delimited but merge into one another the second stage gradually manifesting itself as the nervous symptoms develop following injury to the nervous tissue from the inflammatory changes in the lymphatics of the brain and spinal cord (Blacklock and Yorke)

Rhodesian sleeping sickness is caused by *Trypanosoma rhodesiense* In the human host the morphology of the species is identical with that of *Trypanosoma gambiense* In subinoculated small laboratory animals however the nuclei of a varying percentage of the short forms migrate posteriorly to the

1 Gm (15 grains) of quinine daily in doses of 0 3 Gm (5 grains) each for two days and then follow immediately with a course of atabrine described below A complete course of quinine consists of 1 Gm (15 grains) daily for seven days in divided doses of 0 3 Gm (5 grains each) This usually suffices to eliminate all parasites from the circulating blood in cases of vivax and quartan malaria In *falciparum malaria* the effective dose is somewhat larger, 0 3 Gm (5 grains) four times daily for seven days In any instance therapy should not be discontinued until the patient has had five days of normal temperature with negative blood smears for the same period of time The patient should then be advised that this may constitute the final treatment but that a certain percentage of individuals will experience a relapse which in practically all instances is less severe than the initial attack The treatment for the relapse is the same as for an initial attack The appearance of a malaria attack following treatment is not always a relapse but may represent a reinfection with a different parasite This being especially true in regions where malaria is endemic emphasizes the necessity for microscopic diagnosis For patients unable to tolerate quinine by mouth it should be given intravenously as quinine di hydrochloride in very dilute solutions 0 3 Gm (5 grains) in 10 cc of sterile distilled water Ringing of the ears dizziness or slight deafness following quinine do not constitute symptoms of alarm but a real idiosyncrasy is recognized by an immediate urticarial rash dyspnea or cyanosis and warrants immediate withdrawal of the drug

Atabrine—Atabrine is a synthetic drug and a quinoline derivative Its use is indicated in vivax and quartan malaria but is especially efficacious against the *asexual* parasites of falciparum malaria A course of treatment of atabrine consists of 0 1 Gm (1½ grains) three times a day for five days Whenever possible it should be given by mouth With this treatment vivax and quartan malaria respond in practically the same manner so that usually no parasites are found after the third dose Falciparum malaria responds more slowly The parasites may not disappear until after the fourth dose or later and there is little or no effect against the gametocytes of this parasite As a rule fewer relapses occur after atabrine than quinine therapy, although the difference in the results between the two drugs is not marked Where oral medication is not feasible the drug can be given intramuscularly in daily doses of 0 2 Gm (3 grains) Practically all patients develop a temporary yellow discoloration of the skin following its use which is due to deposition of the dye within the tissues and is not to be regarded as a toxic symptom There have been occasional reports of temporary mental derangement following atabrine although this finding is very infrequent There are also reports to the effect that certain preparations occasionally produce nausea and vomiting This complication can be avoided or lessened by taking the drug immediately preceding a meal

Plasmoquin—This synthetic drug has its particular effective action against the gametocytes of malaria infections particularly falciparum malaria It should not be used alone in the treatment of acute attacks of malaria but in conjunction with quinine or following the administration of atabrine When given with quinine it reduces the number of relapses which usually follow vivax or quartan malaria The simultaneous administration of atabrine and plasmoquin is not advised because there is a *tendency* to increase the toxicity of each Therefore when atabrine is the drug of choice plasmoquin should be withheld until the week following Because of its toxicity plasmoquin should be given under the direct supervision of the physician in biweekly doses of 0 0? Gm (⅓ grain) until gametocytes have disappeared

The general treatment consists of simple measures aimed at keeping the patient comfortable especially during the acute paroxysms In infections complicated by vomiting or diarrhea special effort should be made to maintain the normal fluid level It is advisable that convalescent patients receive iron in any of the available forms as it is extremely beneficial in the restoration of the hemoglobin deficiency Many favorable reports have followed the use of liver therapy There are occasional reports advising splenectomy in chronic cases with gross enlargement of the spleen but this practice

are not advised In second stage conditions the doses per kilo of body weight should be increased to 0 09 Gm for children 0 07 Gm for young adults and 0 06 Gm for adults In advanced second stage cases two or three large doses should be given at five-day intervals followed by a rest of ten to fourteen days The maximum dose for adults should be 4 Gm The drug may be given intravenously or intramuscularly The severe toxic reaction is optic atrophy

Orsanine or Fourneau 270 is extensively used in French Equatorial Africa and is believed by the French workers to be equal to tryparsamide which it has partially replaced It is similar to tryparsamide in dosage toxicity and effect on the optic nerve The greater activity of orsanine is believed to be due to the large proportion which is reduced to the active form and not to any greater power of penetration into the cerebrospinal fluid

Neocryl is well tolerated in weekly doses from 2 to 4 Gm Comparatively few patients have been treated with this drug In first stage patients the results compare favorably with tryparsamide but in the second stage cases the results have been unsatisfactory

Germanin or Bayer 205 moranyl known in Great Britain as antrypol and in France as Fourneau 309 is of very great value in the early stages of the disease before involvement of the nervous system probably because of its failure to penetrate readily into the central nervous system The toxic reactions are relatively few transient edema skin rashes pruritus purulent conjunctivitis stomatitis skin rashes and mild peripheral neuritis The drug should be given cautiously to patients with impaired kidney function Bayer 205 may be given intravenously or intramuscularly Various investigators have reported cures after administering a total of about 10 Gm of the drug The exact course of treatment varies with different authorities The usual single intravenous dose for an adult is 1 Gm dissolved in 10 cc of water given weekly for a course of five treatments Some authorities recommend a combined course of germanin and tryparsamide especially in moderately advanced cases

W H TALIAFERRO

SOUTH AMERICAN TRYPANOSOMIASIS

(*Chagas Disease*)

South American trypanosomiasis or Chagas disease is found chiefly in Brazil but has also been found in Guatemala San Salvador, Panama Colombia Venezuela Peru Argentina and Chile The parasite has been found in reduviid bugs in Ecuador Uruguay, Mexico and the United States (California and Arizona) The trypanosome may be primarily a parasite of the armadillo and opossum and only accidentally transmitted to man

Etiology—The causative agent, *Trypanosoma cruzi* when found in the blood has an ordinary trypaniform structure and averages about 20 microns in length The parasites however unlike those of the African types do not reproduce in the blood but invade the tissues and are transformed into typical leishmania like parasites These tissue or leishmaniform bodies are spherical vary from 2 to 4 microns in diameter and exhibit the same structure as the Leishman Donovan bodies found in kala azar or Oriental sore They may be again transformed into trypaniform bodies and reenter the blood The infection is transmitted from man to man or from animal to man by several species of reduviid bugs chiefly *Triatoma megista* The bug receives its infection by ingesting infected blood but whether man is infected by the bite of infected bugs or from the feces of such bugs is not definitely known

Clinical Course—The disease can generally be divided into two stages—acute and chronic The *acute stage* generally lasts twenty to thirty days and is characterized especially in children by fever myxedematous swellings and enlargements of the thyroid and lymphatic glands liver and spleen During this stage the trypaniform parasites are present in the blood and the leishmaniform bodies are found in the tissues If the patient survives this stage the disease becomes chronic and may persist for many years During the *chronic stage* the trypaniform parasites disappear from the blood but the tissue infection with the leishmaniform organisms continues Symptomatically this stage is characterized by the occurrence of various organic syndromes the char

parabasal body to form what are known as posteriorly nucleated forms The course of the disease is similar to that of the Gambian type, except that *Trypanosoma rhodesiense* is much more virulent for man and is much more resistant to treatment *Trypanosoma rhodesiense* is transmitted by *Glossina morsitans* and may be a human strain of the well known *T brucei* of animals In the insect its development is similar to that of *Trypanosoma gambiense* in *Glossina palpalis*, with the exception that it may be completed within fourteen days after ingestion of the infected material

Diagnosis—Although certain clinical symptoms arouse suspicion, definite diagnosis can be made only by demonstration of the parasite This is often difficult because of the scarcity of the parasites in the blood No reliable serologic tests have been devised and cultivation *in vitro* is too difficult to be of any service

Microscopic examination of the blood may be made either with a drop of fresh blood under a cover slip or with a stained smear The former method is preferable because the characteristic agitation of the blood cells by the living trypanosomes facilitates their detection If auto agglutination of the red cells is observed further search is always advisable In suspected cases when none of the organisms can be discovered it is best to examine a large quantity of blood Ten cc may be withdrawn from a vein citrated or oxalated and centrifuged at a low speed to throw down the red cells The supernatant fluid may then be withdrawn, recentrifuged at high speed, and the sediment examined for parasites Often by this method the trypanosomes may be discovered even though they are extremely scarce in the blood Thick films such as are used in the diagnosis of malaria are employed by some workers

Gland Puncture—When the glands (particularly those of the posterior triangle of the neck) are enlarged and soft their tissue fluid almost invariably contains trypanosomes A small quantity of this may be sucked out with a sterile dry hypodermic needle In old or treated cases where the glands are often sclerosed this method of course is unsuccessful

Lumbar puncture is of value in the second stage of nervous involvement because the sediment from centrifuged spinal fluid often contains trypanosomes Since the cell content of the spinal fluid increases with cerebrospinal involvement, the cell count may furnish a rough index of the extent of cerebrospinal invasion

Inoculation into Susceptible Animals—Laboratory animals such as rats mice guinea pigs rabbits and monkeys (*Macacus* and *Cercopithecus*) may be inoculated subcutaneously or intraperitoneally with suspected blood gland fluid, or spinal fluid, and their blood examined for trypanosomes

Trypanosoma gambiense and *T rhodesiense* can be differentiated by the posteriorly nucleated forms which develop in subinoculations of the Rhodesian strain into the smaller laboratory animals In lieu of this the characteristics of geographic distribution, virulence and resistance to chemotherapeutic agents are of value

Treatment of the diseases has greatly advanced since 1920 when tryparsamide and Bayer 205 were introduced into clinical use While the number of metallic and organic drugs which have been studied is large the number of compounds actually employed in therapy is small (see Findlay 1939, for a detailed account of these trypanocides) The more important in clinical use are (1) tryparsamide and (2) orsanine or Fourneau 270 among the pentavalent arsenicals, (3) neocryl a trivalent arsenical and (4) germanin or Bayer 205, or the French equivalent moranyl or Fourneau 309 Of the older drugs atoxyl tartar emetic, and antimony trioxide are still used either singly or to reinforce treatment with the drugs now in general use Their efficacy is practically limited to the earlier stages of the Gambian disease and with these three drugs prognosis of the Rhodesian disease in all stages and the Gambian infection in the latter stages is practically hopeless

The efficacy of tryparsamide in the treatment of trypanosomiasis probably lies to a large extent in the ease with which it penetrates the central nervous system In first stage cases according to Chesterman six, to eight weekly injections should be given The dose per kilo of body weight in children should be 0 07 Gm for young adults 0 055 Gm and for adults 0 045 Gm Second courses

Russian Turkestan and South America A few cases have been reported in the United States but all had contracted the disease in parts of the world where kala azar is endemic In India in the province of Bihar over 90 000 received treatment in one year

The disease is far more common in the country or villages than in cities In India and China the heavily infected areas are in the low lying alluvial plains In China the most heavily infected villages are in Kiangsu along the old bed of the Yellow River In some villages the disease assumes epidemic proportions Three hospitals in this area treat altogether over 5000 kala azar patients a year

There is no difference in sex incidence The greatest number of cases occur between the ages of five and fifteen After this the incidence falls as the age advances It is rare in individuals over sixty years of age

Etiology —The fact that in cultures and in some insects *Leishmania donovani* grows into a flagellate resembling the common insect herpetomonads suggests that an insect is an essential host In the sand fly (*Phlebotomus argentipes*) there is a remarkable development into flagellates which are virulent and which may escape from the proboscis during feeding Most investigators believe that the sand fly is the transmitting agent Thousands of attempts however have been made to transmit the disease to hamsters by means of the sand fly and in nine they have been successful For many years along the Mediterranean coast dogs have been under suspicion as the reservoir host of human kala azar Both in Malta and Peiping a few naturally infected sand flies have been found in association with infected dogs *L canis* and *L donovani* appear to be identical and the evidence at present available supports the view that in North China the dog is the reservoir of the disease It has been possible to transmit the infection by the oral route Leishmania has been demonstrated in the stools urine prostatic fluid and gastric contents and in the nasal and oral secretions of kala azar patients

Protozoology —There are two phases of the parasite the so-called "Leishman Donovan body" of the mammalian host, and the flagellate phase The Leishman Donovan body which is round or oval or piriform in shape contains two very characteristic structures by which identification of this body" in smears is made These are the nucleus and kinetoplast The nucleus which is almost spherical is about one third the diameter of the organism and often lies pressed against the membrane The kinetoplast is usually seen as a rod lying with its long axis directed toward the nucleus

In Romanowsky stained films the nucleus appears as a mass of red granules while the kinetoplast, which is a more solid compact body takes a deep reddish-purple tint When spherical, the diameter of the parasite is from 1 to 3 microns—when ovoid the long diameter is from 2 to 5 microns and the shorter from 1.5 to 2.5 microns

The flagellate form is a fusiform body observed in culture and in certain insects particularly in the sand-fly The general morphology of the flagellate stage is that of a typical Herpetomonas *i.e.*, it is an organism possessed of a single flagellum which rises in connection with a kinetoplast situated anteriorly to the trophonucleus and having no trace of an undulating membrane The usual length of the body of the parasite varies from 9 to 16 microns The breadth is usually about 1.5 microns The length of the flagellum is frequently about the same length as the body Rogers (1904) was the first to cultivate the organism and thus discover its flagellate phase It is most easily cultivated on the Novy McNeal Nicolle (N N N) medium at 22 C

Animal Inoculation —Hamsters (*Cricetus griseus*) white mice squirrels and dogs can be experimentally infected with this organism Some of these species tend to recover spontaneously from the infection Rabbits and guinea pigs are resistant.

Morbid Anatomy —Kala azar is essentially an invasion of the reticulo-endothelial system of the body by *Leishmania donovani* The parasites are taken up by the reticulo endothelial cells where they develop until the cell becomes distended and bursts discharging numerous parasites into the blood stream Here they are taken up by the mononuclears or clasmatocytes and also by the leukocytes The tissues react to the infection by a proliferation of the reticulo endothelial system There is also an increase in plasma cells in the spleen and bone marrow The increase in the cells of the reticulo endothelial system is so great as to cause a rapid increase in the size of the spleen The endothelial and Kupffer cells of the liver are also parasitized resulting in an enlargement of this organ The parasite is to be found in largest numbers where there is reticulo endothelial tissue that is in the spleen liver bone marrow and lymph nodes and in the endothelial lining of the small blood vessels throughout the body

In the most advanced infections the parenchymatous cells of the liver and adrenal cortex become parasitized and severe

acter of which depends upon the systems and organs chiefly involved Considerable doubt exists as to whether all of the symptoms described by Chagas are actually due to *Trypanosoma cruzi* or to superimposed conditions

Diagnosis—Diagnosis can only be made definitely by finding the parasites They are most easily found during the acute stage when the trypaniform organisms are still in the blood and when their presence can be demonstrated by microscopic examination or injection into susceptible laboratory animals Parasites can be occasionally found in small numbers during the chronic stage, but whether this is due to the chronic infection or to reinfection is not known In endemic regions the trypanosomes are sometimes accidentally discovered in thick blood films prepared for malarial surveys Gland puncture has not been of any value in this infection but when there is cerebrospinal involvement the parasites have sometimes been found after lumbar puncture Attempts to recover the leishmania stages by puncture of the various muscles and organs have not been successful Complement fixation tests (Machado reaction) have been devised and preliminary work indicates that they are of value Kelser has recently prepared an antigen of high potency from artificial cultures of the parasites

Treatment—The usual trypanocides are not effective and so far no satisfactory drug treatment has been devised A number of patients apparently recover spontaneously

W H TALIAFERRO

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LEISHMANIASIS

THREE diseases kala azar cutaneous leishmaniasis and American leishmaniasis may be considered under the heading *Leishmaniasis* as the parasite in each case is morphologically identical The three diseases, however differ clinically and have in general a different geographic distribution

E B STRUTHERS

KALA AZAR

(*Visceral Leishmaniasis Dumdum Fever Black Fever*)

Definition—Kala azar is an infectious disease characterized by enlargement of the spleen and usually of the liver long continued irregular fever, anemia and leukopenia with progressive loss of weight and strength It is caused by a protozoon *Leishmania donovani* which is present in the spleen, liver peripheral blood and the cells of the reticulo endothelial system

History—The disease is known to have existed in India since 1869 it was however not accurately described until Clark in 1882 reported an epidemic that had been raging in Assam for some years He states that there is a fever of malarial poisoning known among the natives as kala azar or black sickness from the darkened colour which the skin assumes in chronic cases Sporadic cases with similar symptoms were also observed in Italy and the Greek islands The disease was not definitely differentiated from malaria and other fevers until Leishman in 1903 described the parasite found in the spleen of a soldier who had died of a long continued fever contracted at Dumdum in Bengal The same year Donovan in Madras independently found the parasite in spleens postmortem and in a living patient by splenic puncture Laveran and Mesnil named the organism *Leishmania donovani*

Incidence—The most heavily infected areas are in Eastern India and in North China It has been found in all the countries which border on the Mediterranean the Sudan West Africa Iraq Southern Russia

neostam and urea stibamine the initial dose should be 0 05 Gm and the maximum dose 0.2 Gm or 0 25 Gm continued until a total of 2 6 or 2 8 Gm has been given In children the initial dose of neostibosan is 0 05 Gm and the maximum dose 0 2 Gm Very small children should be given doses proportionate to their weight Fewer reactions occur in children than in adults These drugs may produce such toxic effects as fever cough nausea vomiting lymphadenitis and headache After evidence of toxic action the amount given at the next injection should be reduced or the interval between the injections lengthened If the toxic symptoms are serious it is advisable to substitute one of the other pentavalent compounds

A new antimony compound solustibosan is less toxic than neostibosan It has the advantage of forming a stable solution and may if necessary be injected intramuscularly A number of patients have been successfully treated with 4 4 diamidino stilbene Symptoms of shock after the injections are not uncommon but no deaths have been reported

With the pentavalent antimony compounds a recovery rate of 90 per cent is to be expected About 3 per cent die during treatment and 6 per cent relapse The relapse rate bears a relation to the total amount of the drug injected

A diet adequate in protein and vitamins is advisable Liver and some form of iron should also be prescribed

In a patient who progresses favorably during treatment the temperature returns to normal there is an increase in weight and strength and a decrease in the size of the spleen and there is also an increase in hemoglobin erythrocytes and leukocytes An increase in leukocytes is a good prognostic sign but there is no way to foretell at the end of a course of treatment whether a patient will or will not continue to improve until all the parasites are exterminated The only satisfactory method is to reexamine the patient at the end of one three and six months The only proof of cure is freedom from symptoms and signs of the disease for at least six months

Post kala azar dermal leishmaniasis which was first described by Brahmachari in 1922 is a sequela of generalized leishmania infection The dermal lesions make their appearance from one to two years after treatment after all signs of the visceral infection have disappeared The skin eruption appears as depigmented areas erythema or butterfly rash and nodules More rarely it is of the verrucose papillomatous or xanthoma type *Leishmania donovani* may be found in the skin lesions but not by spleen puncture

E B STRUTHERS

CUTANEOUS LEISHMANIASIS

(Oriental Sore Aleppo Boil Delhi Boil)

Definition —Cutaneous leishmaniasis is an ulcerating granuloma of the skin caused by the protozoal parasite *Leishmania tropica*

History —The same month that Donovan described the etiologic agent of kala-azar an Armenian was admitted to the Massachusetts General Hospital in Boston presenting what was diagnosed as tropical ulcer In the excised tissue, Wright found the parasite now called *Leishmania tropica*

Incidence —The disease is widely distributed The names mentioned above suggest parts of the world where the disease is common It is found in India Persia Palestine Africa and countries around the Mediterranean Sea in Costa Rica Brazil and Peru

Etiology —The *Leishmania tropica* cannot be distinguished microscopically from *L donovani* of kala azar already described Dogs in Persia and Algeria have been found naturally infected There is little doubt that the usual vector is the sand fly (*Phlebotomus*) though it is possible that houseflies may carry *L tropica* and so infect open wounds It may be directly inoculated from man to man

Symptoms —The incubation period varies from a few weeks to several months The lesion may appear on any exposed part of the body usually on the upper extremity or on the face It begins as a small red papule (single or multiple) which gradually enlarges becomes purplish in color and soft in the center The surface breaks down and an ulcer with round edges is formed The sores are usually about 1 inch in diameter In the nonulcerating variety fluid obtained by puncture will yield many parasites To find parasites in ulcerated sores it is well to

areas, schistosomiasis is not found this test has been found of great value in ruling out febrile conditions with splenomegaly due to malaria and other diseases In this test 0 02 cc of blood is collected in a Sahli hemoglobin pipet and emptied immediately into a small test tube containing 0 6 cc of freshly distilled water The contents of the tube are quickly mixed and the tube allowed to stand without further shaking At the end of five minutes, a haziness or cloudiness should be present in all positive tests and the tests that show a definite settling or fairly complete sedimentation of the precipitate within fifteen minutes are considered strongly positive those in which this change does not occur until after fifteen to thirty minutes moderately positive those between thirty and sixty minutes weakly positive and those that show only a haziness and a very fine precipitate but no sediment even after one hour very weakly positive Only strongly positive tests are of value as other diseases may give weakly positive results Leukemic blood, owing to numerous undissolved nuclei of the leukocytes will give a false positive A drop of acetic acid will dissolve the globulin but not the cell nuclei

The Formalin Test (Aldehyde Test) — One drop of 30 per cent formalin is added to 1 cc of clear serum in a small test tube and immediately mixed by shaking Serum from well established cases of kala azar (three or four months or more) will become solid and opaque like the 'white of a hard boiled egg in less than half an hour If the opacity is only partial (opalescent) the result is doubtful and if no change occurs within twenty four hours the result is considered negative Gel formation an associated factor is not by itself of any value in the diagnosis of kala azar

Antimony Test —On adding 2 drops of the patient s serum to 1 cc of 0 5 per cent solution of urea stibamine or other pentavalent antimony compound a heavy precipitate is formed

These tests are positive in about 90 per cent of kala azar sera in which they demonstrate a marked increase of euglobulin When negative in a patient with an enlarged spleen they are of definite value in excluding kala azar

Differential Diagnosis —Kala azar must be differentiated from the following diseases malaria typhoid fever schistosomiasis syphilitic splenomegaly tuberculosis undulant fever and bacterial endocarditis The water formalin and antimony tests are often positive in bacterial endocarditis In any obscure fever, associated with splenic enlargement and progressive leukopenia, the possibility of kala azar should be considered

Prognosis —Without treatment it is probable that over 90 per cent of kala azar patients die within two or three years By the introduction of antimony in treatment, especially the pentavalent antimony compounds the rate of recovery is now as high as the former death rate Occasionally those who without treatment survive cancrum oris or pneumonia are found to have also recovered from the primary disease

Treatment —Antimony discovered in 1908 to be lethal to trypanosomes was found by Di Cristina and Caronia in 1914 to cure cases of kala azar in children They injected a solution of tartar emetic intravenously Its value in kala azar was soon confirmed by Rogers, Muir and others in India Previous to the introduction of antimony many drugs had been tried without success Since that time thousands of patients have been cured with tartar emetic or sodium antimony tartrate The course of treatment however with these drugs was long and tedious extending over a period of three or four months Reactions were not infrequent and about 10 per cent of the cases treated died from toxic reactions or complications caused by the antimony

For these reasons one of the newer pentavalent antimony compounds should always be used Their toxicity is almost one twentieth that of tartar emetic reactions are fewer a cure can be effected in three weeks and the recovery rate is considerably higher The compounds which have been most used are neostibosan urea stibamine and neostam All are given by intravenous injection The drug is dissolved in freshly distilled water to make a 5 per cent solution Neostibosan may be given in daily injections but is usually given on alternate days in the following doses 0 1 Gm 0 2 Gm 0 25 Gm or 0 3 Gm If no reactions occur the maximum dose is continued until for a patient weighing 100 pounds 3 Gm has been given With

not only asexual propagation but maturation and fertilization of the sex cells are carried out with a brief extrinsic phase for the production and ripening of the sporozoites

The Sarcosporidia and species of *Toxoplasma* have previously been placed by some investigators in the Class Sporozoa although there appears to be little or no justification for this view These organisms should rather be grouped in a category of *Sedes Incertae* but for convenience will be considered briefly as an Addendum to this Class group

The malaria parasites and human malaria are presented elsewhere in this volume (p 374)

ERNEST CARROLL FAUST

COCCIDIOSIS

(*Coccidiasis*)

Coccidiosis is an infection caused by sporozoan parasites belonging to the genera *Isospora* and *Eimeria* While several species of these organisms have been reported from man all except one (*Isospora hominis*) have on careful scrutiny been found to be spurious parasites taken into the human digestive tract in infected fish

Isospora hominis has been inadequately studied due for the most part to its relatively uncommon occurrence in areas where modern medical examination is available in part to the moderate symptoms usually associated with its presence and finally to the fact that no postmortem data are available The writer has had the opportunity of observing five clinical cases on which this presentation will be primarily based

History —According to Virchow (1860) *Isospora hominis* was probably discovered by Kjellberg earlier in that year in the villi of the human ileum This was confirmed by Eimer in 1870 The 208 human infections reported have been from the Mediterranean countries from several foci in East, West, South and Central Africa, China, Indo-China, the Philippines Dutch East Indies India, South America Hawaii and the United States

Morbid Anatomy —The schizogonic phase of the life cycle in man is undescribed but is believed to occur in the villi of the lower portion of the ileum where the encysted fertilized eggs (*oocysts*) are formed pass down the bowel and out in feces They are slightly irregular elongate ovoidal objects measuring 20–33 by 10–19 microns and contain a single spherical cell In fecal samples at warm room temperatures the single cell soon divides into two smaller spheres (*sporoblasts*) within each of which there are formed four crescentic *sporozoites* The *sporocyst* with its eight sporozoites is now infective for man and if taken into the mouth in feces-contaminated food or drink will presumably hatch in the small bowel and initiate a new infection

Clinical History.—The infected patients seen by the writer in China gave a common history each sought relief from a severe watery mucous diarrhea of several days standing They were put to bed placed on a bland diet and in the course of ten to fifteen days had completely recovered Follow up examination from one to three months later confirmed this finding Parallel with the clinical observations the oöcysts were very plentiful in the stools of the patients on admission to the hospital diminished gradually and before the patients discharge had completely disappeared There is thus some evidence indicating that rest and diet contributed to a spontaneous evacuation of the organisms from the human body Although many species of *Isospora* have been described from domestic and wild animals none is morphologically similar to *I hominis* Thus the relatively few sporadic cases of human infection remain epidemiologically unexplained (Magath 1935)

Prevention presumably consists in care not to take food or drink contaminated with *I hominis* spores

ERNEST CARROLL FAUST

SARCOSPORIDIOSIS

This infection is produced by the organisms belonging to the genus *Sarcocystis* a member of the group SARCOSPORIDIA the systematic position of which is undetermined It is even probable that these parasites are not protozoan forms at all and may possibly be fungi like pecies of *Rhinosporidium* which were previously classed as protozoa *Sarcocystis* de cribed under several species names is a fairly widespread infection in reptiles birds and mammals including sheep cattle horses and rodents

Morbid Anatomy —One species *Sarcocystis lindemanni* Rivolta 1878 has been

obtain fluid from the tissues below the contaminated surface After a variable period of three months to a year healing begins A slightly depressed disfiguring scar remains One attack confers immunity

Treatment—When possible excision with the electrocautery is often the method of choice Good results are claimed by applying sulfapyridine or Uleron directly in powder form to the sore after cleansing with saline solution A 2 per cent ointment of antimony tartrate of fuchsin paint may be applied locally Berberine sulfate 3 or 4 cc of a 1 per cent solution may be injected into the tissues about the ulcer Two to 5 injections often effect a cure Carbon dioxide snow, x rays and ionization are all said to be useful In the epidemic at Quetta sores were scraped under gas anesthesia followed by the application of pure carbolic acid and a cover of elastoplast The cover was left in position for two weeks

E B STRUTHERS

AMERICAN LEISHMANIASIS

(Mucocutaneous Leishmaniasis Nasopharyngeal Leishmaniasis Espundia Brazilian Leishmaniasis)

Definition—American leishmaniasis is a type of cutaneous leishmaniasis which differs clinically from oriental sore in that it affects the mucous membranes of the nose and throat in from 10 to 20 per cent of the cases

Incidence—With the possible exception of Chile the disease occurs in every country of South America It is especially prevalent in Brazil Peru and Bolivia In Paraguay it is said to have assumed epidemic proportions

Etiology—As in oriental sore scrapings from the lesion show the presence of a parasite similar to *Leishmania donovani* or *L tropica* which has been called *L braziliensis* The sand fly again is the probable transmitter

Symptoms—The sore may appear on any exposed part of the body and presents the appearance of oriental sore or it may begin on some mucous surface where it produces a fungating ulcer The sores infiltrate the deeper tissues causing destruction of the nose and parts of the face The pharynx and larynx may be affected

Treatment—The treatment is the same as that for oriental sore Sodium arsenite 0 005 Gm three times a week or 0 01 Gm twice a week intradermally has been recommended

E B STRUTHERS

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SPOROZOAN INFECTIONS

SPOROZOAN infections are produced by the one celled (or a cellular) animals belonging to the Class SPOROZOA All members of this Class are parasitic Some are in invertebrate hosts probably many more in vertebrates and a few very important ones produce disease in man All of these parasites require an alternation of asexual reproduction (*schizogony*) and sexual reproduction (*sporogony*) to complete a life cycle The two important groups of Sporozoa which parasitize man are the Hemosporidia and the Coccidia In the Hemosporidia all or part of the asexual stage occurs in the blood cells of the intermediate host while maturation of the sex cells fertilization and sporozoite production take place in the definitive host The most notable examples of the Hemosporidia parasitizing man are the malaria parasites of which man is the intermediate host and the *Anopheles* mosquito is the definitive host In the Coccidia only a single host is required in this host

CILIATE INFECTIONS

BALANTIDIASIS

(*Balantidiosis*)

THE CILIATA constitute a distinct class group of the PROTOZOA They are unicellular organisms which have numerous meridional rows of relatively short threadlike extensions of their cytoplasm the *cilia* anchored in basal granules within the limiting membrane or *pellicle* These cilia are organelles of locomotion and those near the anterior end also frequently serve to bring food into the *cytostome* or primitive mouth which lies to one side of the anterior extremity Ciliates have a large sausage-shaped *macronucleus* and at least one *micronucleus* and multiply by transverse binary fission Most species characteristically undergo conjugation a reciprocal exchange of nuclear material Some species encyst when environmental conditions are unfavorable to growth and propagation The great majority of ciliates are free living forms but a few are obligatory parasites Of these latter only one *Balantidium coli* is medically important

History.—*Balantidium coli* (Malmsten 1857) was first seen by Malmsten in 1857 in the stools of two Swedish patients who were suffering from dysentery Since its discovery this parasite has been reported as having an extensive distribution in Northern Southern and Eastern Europe the U S S R, including Siberia China, Ceylon Java and the Philippines Egypt, the Sudan and Abyssinia several of the countries of South America, Honduras Cuba and Puerto Rico and in several of the United States While most species of monkeys harbor a natural infection of *B coli* human balantidiasis is almost invariably linked to association with pigs which are the important reservoir

Life Cycle—*Balantidium coli* is the largest of the protozoan parasites of man ranging in length from 50 to 100 microns and in breadth from 40 to 70 microns The living organism is a sturdy ovoidal glassy green object which is covered with many rows of cilia arranged in a slightly oblique pattern from upper left to lower right (as seen under the compound microscope) A *cystostome* or cell mouth for the intake of food is readily observed somewhat to one side of the anterior extremity At the aboral end is a primitive anus Within the body is a large slightly curved *macronucleus* and near the center of its concave margin a minute *micronucleus* Numerous food and contractile vacuoles constitute the other conspicuous organelles of the parasite By means of its multitude of cilia beating synchronously *B coli* moves ahead in a slightly spiral path It avidly ingests particulate food stuffs including starch grains It divides by transverse binary fission In a film of semi formed or liquid stool the motile *Balantidium* may be observed under the microscope to plough through the medium then become relatively quiescent round up partially retract its cilia and secrete a tough cyst wall around itself It does not multiply during the cystic stage

Morbid Anatomy.—As a parasite of man *Balantidium coli* invades the wall of the large bowel especially in the region of the cecum Its entry into the tissues is primarily mechanical although it probably possesses some lytic properties In uncomplicated infections the lesion produced is cup like or flask like but due to its relatively larger size the opening is larger than that produced by *Endamoeba histolytica* At times there may be deep pockets or burrows considerably below the muscularis mucosae and rarely the organisms gain entry to mesenteric blood vessels However there is apparently no record of *Balantidium* setting up foci of infection in the liver In uncomplicated lesions there is no evidence of local or generalized host cellular reaction to the invader except attempts of fibroblastic repair In chronic balantidiasis the lesion is frequently complicated by bacterial invaders which call forth a concentration of neutrophilic leukocytes and small monocytes in the immediate vicinity

Clinical History—The usual patient harboring *B coli* gives a history of association with pigs from which reservoir the infection has undoubtedly been contracted as a result of the ingestion of cysts of the organisms taken into the mouth on contaminated fingers food or drink soiled with pig s dung These patients either have an inapparent infection (*i e* are carriers) or have a moderate to severe water mucous diarrhea usually without macroscopic blood Constipation may alternate with diarrhea The writer has seen these two types on several occasions in China Panama Puerto Rico and in the Charity Hospital in New Orleans and knows of other infections in Arkansas

reported on nine occasions from man It parasitizes the striated muscles and connective tissue rarely the unstriated muscles of its host, developing in elongated spindle shaped membranous capsules having rounded ends and internal septa Within the capsules are myriads of sickle shaped spores or *sarcocysts* which are most plentifully developed in muscles of the throat chest diaphragm and abdomen The mother capsules measure up to 25 mm in length the spores 12–16 by 4–9 microns The exact manner in which man becomes infected is unknown but it is believed that the ripe spores are accidentally swallowed in food or drink and by means of a digestive ferment (*sarcocystin*) gain entry to the musculature *via* the intestinal wall

Diagnosis can be made by biopsy and at autopsy by demonstration of the capsules with their spores This infection should not be confused with trichinosis (p 411) which also parasitizes striated muscles In extensive involvement of the musculature some degeneration may occur and a mild cachectic state may develop There is no specific *treatment*

Prevention consists in care not to ingest uncooked meat or possibly raw water in which infected dead reservoir hosts may have disintegrated

ERNEST CARROLL FAUST

TOXOPLASMOSIS

Until very recently this clinical entity was poorly understood and poorly defined The infection is produced by species of the genus *Toxoplasma* organisms which have been recovered from body fluids and exudates but typically reside intracellularly in mononuclear and epithelioid cells nerve cells muscle fibers endothelial cells of capillaries and polymorphonuclear and eosinophilic leukocytes Dozens of species of *Toxoplasma* have been described based primarily on the vertebrate hosts they parasitize but there is practically no proof that they represent other than strains of the same species They are minute (2–6 by 1.5–2 microns) distinct oval pyriform rounded crescentic or elongated protoplasmic masses each with a more or less central nucleus They occur singly or in clusters in the host cell and multiply by repeated binary fission

History.—The three earlier records of human *Toxoplasma* infection (*T pyogenes*) reported by Castellani (1914) Federovitch (1916) and Chalmers and Kamar (1920) are today not subject to verification. The more recent reports (Janku 1923 Torres 1927 Hertig, 1936; Wolf and Cowen 1937 Richter 1938 Wolf Cowen and Paige 1939 Pinkerton and Weinman 1940 Sabin, 1939 1941 and Pinkerton and Henderson, 1941) involve infants children and adults suffering from fatal or severe encephalomyelitis and adults with a syndrome simulating fatal rickettsia disease In at least two of these cases guinea pigs became positive after inoculation with material from the living patient or at necropsy and developed characteristic lesions

It is possible that inapparent toxoplasmosis may be relatively common in human beings and in various animals which then may serve as carriers although the method of transmission is unknown In clinical cases the *prognosis* is almost invariably grave There is no *specific treatment* although sulfathiazole and sulfapyridine have been demonstrated by Sabin and Warren (1941) to have a curative effect on toxoplasmosis in mice Protection tests in laboratory animals suggest the possible development of protective vaccines

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Among the flatworms there are two classes containing important human parasites These are the TREMATODA or flukes and the CESTOIDEA or tapeworms

ERNEST CARROLL FAUST

TREMATODE OR FLUKE INFECTIONS (*Trematodiasis*)

Trematodiasis is an infection with species of TREMATODA (Flukes), which possess the general characteristics of the PLATYHELMINTHES but with the following restrictions the ciliated epithelium is confined to the larva (*miracidium*) hatched from the egg typically flukes have a mouth surrounded by a muscular sucker a pharynx esophagus and a pair of intestinal ceca which end blindly in the subdistal portion of the body All flukes parasitizing man have a complicated life cycle involving a minimum of three generations and obligatory utilization of certain species of snails (or other molluscs) as intermediate hosts The larval stage hatched from the egg (*miracidium*) actively invades the appropriate snail in which a two fold multiplication occurs The tailed larva emerging from the snail (*cercaria*) becomes a free living aquatic form and has one of three recourses depending on the species of fluke It may directly infect man by the skin route (blood flukes) it may crawl onto aquatic vegetation drop its tail and excyst on the surface of the plant (sheep liver fluke) it may penetrate into the soft tissues of certain animals where it encysts (Chinese liver fluke) In the latter two groups man acquires the infection by ingesting raw or inadequately cooked plant or animal food infected with the respective cysts

Most flukes infecting man are hermaphroditic and possess two distinct suckers one surrounding the mouth and a blind acetabulum on the ventral side of the body These species are referred to as *distomes* and their infection is properly designated as *distomiasis* Important exceptions are the blood flukes or *schistosomes* which are unisexual (*i e* diecious) Infection with these latter species is designated as *schistosomiasis*

ERNEST CARROLL FAUST

INTESTINAL DISTOMIASIS

Several species of flukes parasitize the digestive tract of man in most instances the small bowel where the worms are attached to the mucosa by means of their suckers

Fasciolopsis buski —The large fleshy fluke *Fasciolopsis buski* is an important parasite of man (and the pig) in the neighborhood of the China Sea the Southern Pacific Ocean Burma and Eastern India It lives primarily in the levels of the duodenum and jejunum These flukes measure 20 to 75 mm long 8 to 20 mm broad and 0.5 to 3 mm in thickness They lay large colorless transparent thin shelled ovoidal eggs (measuring 130–140 by 80–85 microns) which have a minute operculum They mature only after they have been evacuated in feces into fresh water After several days a miracidium hatches from each egg seeks out and penetrates into its appropriate snail host and undergoes a two fold multiplication within the snail The cercariae which are shed from the snail a few weeks later crawl onto and encyst upon the seed pods of the water caltrop bulbs of the water chestnut roots of the lotus water bamboo or other aquatic plants Man becomes infected when he peels off the hull or skin of these plant products between his teeth and lips before swallowing the raw foodstuff

Symptoms —Wherever the adult worm is attached to the intestinal mucosa there is first a focus of inflammation later a necrotic center with hemorrhage and frequently abscess formation Many worms attached near together at one level of the bowel may produce an acute obstruction Towards the end of the incubation period of about 90 days there is a toxic diarrhea with hunger pains Heavy infections may simulate peptic ulcer and the patient may become asthenic Generalized toxemia is usually manifested in the form of edema particularly of the face abdominal wall and lower extremities Ascites develops in severe infections especially in children Generalized abdominal pain is frequent The diarrhea continues the stool becomes foul smelling and contains much undigested food Anorexia nausea and vomiting are characteristic Death is commonly due to anasarca Most of the patients have a marked leukocytosis with absolute eosinophilia but some

and Kentucky At least one endemic focus of human balantidiasis has been reported from a mental hospital in the United States, *suggesting that the infection is more widespread in this country than has been as sumed* Occasionally severe *balantidial dysentery* with the copious discharge of blood has been reported Even if there is only shallow invasion of the colon and no characteristic postmortem evidence of invasion the bowel mucosa may be hyperemic with superficial necrosis and hemorrhage

In most patients balantidial diarrhea or dysentery is accompanied by abdominal colic tenesmus nausea and vomiting loss of appetite, headache insomnia muscular weakness and loss of weight due to dehydration and poor digestion and absorption of food There is at times a pallor of the skin and mucous membranes and a moderate secondary anemia Usually physical examination will exhibit a tenderness over the colon At times there is an exhausting watery diarrhea or dysentery

Diagnosis of balantidiasis is made by the demonstration of the characteristic trophozoites or cysts of the parasite in the patient s stool These are readily seen under the compound microscope in unconcentrated fecal films and the essential features are well distinguished in fresh films stained with D Antoni s iodine Inexperienced diagnosticians must not mistake for *Balantidium coli* the free living ciliates which grow in old dropping bottles of distilled water or physiologic salt solution and thus may contaminate the fecal films during its preparation *Prognosis* without treatment may be good to poor Some infections probably clear up spontaneously others become chronic and gradually sap the strength of the patient rarely the infection may fulminate and cause death

Treatment of balantidiasis is not particularly satisfactory due perhaps to the fact that in recent years recognized cases have been relatively few and therapy has been mostly sporadic Carbarsone as administered in amebiasis one 0 25 Gm (4 grain) capsule twice daily with meals for ten days, has been helpful in a few instances Chiniofon and vioform should be given adequate trial In case bacillary dysentery complicates balantidiasis sulfonamides should be used as an adjuvant

Prevention consists in meticulous care not to contaminate food or drink with pig's dung and to wash the hands thoroughly before putting them in the mouth

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METAZOAN INFECTIONS

THE METAZOA are animals made up of many cells which in aggregates are usually specialized into tissues and organs performing particular but coordinated functions of the entire organism In this respect the METAZOA differ from the PROTOZOA the one-celled (or a cellular) organisms in which all of the functions are performed by specialized portions of the protoplasm within a single cell unit The parasitic Metazoa are found primarily within the following invertebrate groups the PLATYHELMINTHES or flatworms the NEMATHELMINTHES or roundworms the HIRUDINEA or leeches and the ARTHROPODA comprising the insects and their allies

THE PLATYHELMINTHES

(*Flatworms*)

MEMBERS of this group are invertebrates which have primitively a ciliated epithelium covering the body They have a longitudinal axis with anterior and posterior ends and are bilaterally symmetrical With few exceptions they have either an incomplete digestive tract or none at all There is no body cavity what otherwise would be a body cavity is filled with loose mostly undifferentiated parenchyma cells in the midst of which are located the excretory organs nerve ganglia and trunks and particularly the greatly elaborated genitalia Most of the flatworms are hermaphroditic and thus each individual is a complete reproductive unit

TREATMENT should be instituted if possible before the worms burrow into the intestinal mucosa Caprokol as recommended in *Fasciolopsis buski* infection may be instituted but tetrachlorethylene (C_2Cl_4) is believed to be more specific The adult dosage is 3 cc (45 minims) given in the morning on an empty stomach preceded the night before and followed 2 hours after treatment by Glauber salts purgation (1 ounce or 30 cc dissolved in a glass of water) No food should be permitted until a copious post treatment bowel movement has been obtained Tetrachlorethylene is safe in the absence of alcohol and absorbable fats and should remove all heterophyid worms except those which are deeply imbedded in the bowel wall

PREVENTION consists in the thorough cooking of all fish in endemic areas

Amphistomes —Two other large intestinal flukes referred to as amphistomes because their suckers are at opposite ends of their body have been reported from man *Watsonius watsoni* in West Africa and *Gastrodiscoides hominis* in India Cochin China and among East Indian immigrants in British Guiana Practically nothing is known of their life cycles or epidemiology They produce severe diarrhea indigestion and generalized toxemia with anasarca Caprokol as recommended for *F buski* is likely to prove efficacious for their removal

ERNEST CARROLL FAUST

HEPATIC DISTOMIASIS

Hepatic distomiasis is produced by the sheep liver fluke (*Fasciola hepatica*) and its relatives the Chinese liver fluke (*Clonorchis sinensis*) and its relatives (*Opisthorchis felineus* and *O viverrini*) and by the lancet fluke (*Dicrocoelium dentriticum*)

Fasciola hepatica and its kin *F gigantica* are the largest hepatic flukes measuring about 30 by 13 mm

Life History —As adults they live in the more proximal bile ducts and gallbladder where they lay large colorless transparent, thin shelled unembryonated ovoidal eggs (measuring 130–160 by 63–90 microns) with a minute operculum These eggs hardly distinguishable from those of *Fasciolopsis buski* pass down into the lumen of the bowel and are evacuated in feces They mature in fresh water and undergo an extrinsic life history paralleling that of *F buski* Herbivorous animals grazing on infected swampy pastures are commonly exposed to infection. After the cysts are swallowed with grass and excyst in the duodenum the larvae bore through the intestinal wall into the peritoneal cavity then bore through Glisson s capsule into the liver burrowing through the parenchyma and liver cells until they reach the larger bile ducts Here they grow into adults Sheep liver fluke infection is cosmopolitan wherever sheep are raised Human infections have been reported from Cuba Puerto Rico Mexico Central and South America Southern and Southeastern Europe Africa the U S S R the Near East and the Far East The commonest source of human fascioliasis in Europe and the Western Hemisphere is water cress

Morbid Anatomy —Heavy invasion of the liver by *F hepatica* results in extensive necrosis of the parenchyma (liver rot of sheep) After the worms reach the bile ducts they provoke a hyperplasia of the biliary epithelium with a circumscribing fibrous encapsulation resulting in pressure necrosis of the parenchyma and eventual periportal cirrhosis Symptoms and signs in human infections consist of hepatic colic generalized abdominal rigidity and pain on pressure irregular fever more or less persistent diarrhea leukocytosis with eosinophilia marked anemia anasarca and rarely hemoglobinuria

Diagnosis consists in recovering the characteristic eggs in the feces of persons outside Fasciolopsis endemic areas or from biliary drainage False distomiasis resulting from the consumption of infected sheep or cattle liver must be ruled out *Prognosis* is fair to poor depending on the degree of involvement *Treatment* as outlined by Kouri (1932) consists in the intramuscular administration of emetin hydrochloride (0 03 Gm or ½ grain daily for 17 to 18 days) and has been demonstrated to be quite effective in killing the worms

Prevention consists in meticulous care not to eat raw water cress or other water plants in endemic foci

Other Species —*Clonorchis sinensis Opisthorchis* spp and *Dicrocoelium dendriticum*

chronic cases have a relative lymphocytosis There is no significant anemia

Diagnosis is based on the history of the patient, his residence in endemic foci and the recovery of the characteristic eggs in the feces Prognosis is fair to good in properly treated cases

Treatment—The treatment of choice consists in the administration of caprokol (hexylresorcinol crystoids) in amounts of 0 4 Gm (6 grains) to 1 Gm (15 grains), depending on the age of the patient The drug is administered in 0 2 Gm (3 grains) *hard gelatin capsules* on an empty stomach and is followed in two hours with Glauber salts purgation (one ounce or 30 Gm dissolved in a glass of water) Food must not be taken until four hours after the anthelmintic has been administered In severe infections supportive treatment for the heart may be needed during and immediately following specific therapy Caprokol treatment has a 75 to 100 per cent worm removal value for *F buski* and may be repeated safely within one week

Prevention can be provided by immersing raw vegetables in boiling water for a few seconds The 'seedbeds of the infection may be eradicated by mass treatment of the infected population, together with destruction of the snails by the use of copper sulfate solution (1 to 50 000) in submerged fields where the infected water plants are grown

Other Intestinal Flukes—Several species of flukes small to large and fleshy in character are provided with an incomplete circlet of hooks on the cervical region of their body and are designated as echinostomes

Species belonging to the genera Echinostoma Himasthla Paryphostomum and *Echinochasmus* These have been reported as parasites of the human bowel particularly in the Far East (the Philippines Celebes Malaya India China and Japan) as well as in Roumania and elsewhere

Infection results from eating a variety of raw animal products including snails limpets tadpoles fresh water fish and so on in which the cercariae have encysted The smaller species produce only minor intestinal symptoms but the larger species cause grave symptoms comparable to *Fasciolopsis* infection

Treatment should be carried out along lines indicated for *F buski*

Prevention consists in the thorough cooking of all animal foods

Another type of intestinal distomiasis is produced by many flukes belonging to the family Heterophyidae and represented by the species *Heterophyes heterophyes Metagonimus yokogawai* and their kin which have an extensive distribution in the Far East Egypt, and Southeastern Europe These worms are minute forms at times barely visible to the naked eye are ovoidal, pyriform or nearly cylindrical and possess a peculiar union of their ventral and genital suckers They lay minute ovoidal eggs (measuring 26–30 by 15–17 microns) with a distinct operculum at one end The encysted cercariae are found in the tissues of many species of fresh water and some brackish water fishes

Morbid Anatomy—When various mammals (and frequently birds) eat the infected fish either raw or inadequately cooked these worms gain entrance to the small bowel excyst and attach themselves directly to the lining cells of the glandular crypts or become buried in the cells at times even reaching the stroma of the villi They produce an inflammation of the contiguous or invaded cells with excessive mucous secretion and erosion of cell membranes Worms which have entered the mucous membrane remain there until they die If the number of worms is large and the involved areas of mucosa are considerable a mucous diarrhea may result Until relatively recently these rather mild lesions were believed to constitute the entire story of host tissue involvement but Africa and his colleagues (1935 *et seq*) in the Philippines have demonstrated that in man the minute eggs not infrequently get into the mesenteric lymphatics or venules and are carried to many sites in the body including the myocardium brain spinal cord kidneys etc There they block the blood capillaries and stimulate foreign body reactions setting up trains of symptoms dependent on the organs and tissues involved Thus myocardial invasion may lead to a syndrome simulating wet beriberi or a progressive hypertensive myocarditis brain or spinal cord lesions loss of motor or sensory function at the levels of the lesions

implantations may abscess into the intestine or through the somatic tissues Glandular in volvement may be accompanied by fever Brain tumors the size of a hazelnut or larger may produce a Jacksonian type of epilepsy

Diagnosis is based on finding the characteristic eggs in sputum which is usually blood tinged Because of the macroscopic resemblance of the eggs to minute iron filings there is no serious likelihood of confusing the discharge of pulmonary distomiasis with that of pulmonary tuberculosis or bronchial spirochetosis

Prognosis is usually good unless the worms become lodged in foci like the brain There is no effective treatment Unless reinfected the average patient eventually overcomes the parasites and the lesions heal without dysfunctioning fibrosis

Prevention consists in care not to eat raw or pickled crab or crayfish meat

Ernest Carroll Faust

SCHISTOSOMIASIS

(Bilharziasis)

Schistosomiasis is produced by the schistosomes or blood flukes of which there are three important species of the genus *Schistosoma* parasitizing man over extensive areas of the globe These worms are delicate elongate organisms which live in the portal blood system and collateral venous circulation They are unisexual (*i e* diecious) although during insemination and oviposition the female is held in the long incurved ventral trough of the male (the *gynecophoral canal*) Pairs of the adult worms typically reside in the smaller venules of the bowel wall (*Schistosoma japonicum* and *S mansoni*) or of the vesical and pelvic plexuses (*S haematobium*)

Life History —At the time of oviposition the female extends her thread like anterior extremity as far up into the lessening diameter of the venule as she can then deposits an egg She then contracts a little and lays a second egg just behind the first and another and another until the entire venule is filled with the eggs The pair then back out enter another venule and repeat the process This continues until the entire venous radicle is packed with eggs At the time the eggs are laid or shortly thereafter the larvae (miracidia) within the eggs are fully embryonated and contain unicellular glands elaborating lytic ferments It has been demonstrated that minute droplets of these viscous fluids ooze out through submicroscopic pores in the eggshell into the venule in which the eggs are trapped The digestive action of this ferment, together with the pressure within the venule occasioned by the presence of the eggs weakens and soon ruptures the wall of the venule causing the discharge of the eggs into the perivascular tissues of the bowel or bladder wall Some of these eggs in the mucous or submucous membranes soon effect a passage to the lumen of the respective organ are carried down the bowel or urethra and are evacuated with feces or urine Hemorrhage from the wall of the organ at the time the eggs escape is characteristic of the discharge Thus in the intestinal types there is dysentery in the vesical type hematuria

When the schistosome eggs come in contact with fresh water they hatch and the miracidia swim about and seek out appropriate snails which they enter After two fold multiplication within the snails the cercarial progeny emerge usually with the first bright morning s sunshine These larvae possess a forked tail which characterizes their group When the skin of human beings swimming wading bathing or washing clothes comes in contact with infected water (*i e* containing the fork tailed cercariae) the cercariae become attached drop their tails and penetrate under scaling flecks of epidermis or into hair follicles they burrow down to the peripheral capillary beds as the surface film of water drains off The cercariae are then transported through the afferent blood to the right heart and lungs They slowly squeeze through the pulmonary capillaries are carried through the left chambers of the heart and out into the aorta Only those which get into the mesenteric arteries and pass through to the portal vessels survive All others are filtered out as foreign proteins and die Within the intrahepatic portion of the portal blood the successful blood fluke larvae now for the first time begin to feed on whole blood and grow rapidly Approximately twenty days after

are delicate transparent, narrowly oval flukes which parasitize the distal bile ducts especially near the margins of the liver *Clonorchis sinensis* has a wide distribution in Japan Korea China French Indo China and adjacent areas *Opisthorchis felineus* is prevalent in Siberia, East Prussia South eastern Europe and has been reported from French Indo China *O viverrini* has been found only in Northern Siam *Dicrocoelium dendriticum* has been reported as a human parasite from Siberia Europe, North Africa China and Java *Clonorchis* and *Opisthorchis* are contracted from eating raw fish containing the encysted larvae *Dicrocoelium* infection results from ingesting raw grass containing gelatinous masses of pseudo cysts of this worm

Life History—The encysted larvae crawl up the ampulla of Vater to the distal bile ducts and develop into adult worms Here they may live for 15 to 25 years producing hyperplasia of the biliary epithelium a circumscribing fibrosis of the ducts pressure necrosis of the parenchyma and in heavy infections periportal cirrhosis with ascites Light infections are essentially symptomless moderate infections have a progressive development of hepatic dysfunction with loss of appetite a feeling of fulness of the abdomen diarrhea indigestion edema and hepatomegaly heavily infected individuals suffer from catarrhal cholangitis anasarca tachycardia vertigo tremors abdominal cramps and mental depression resulting from intoxication due to reduced liver function

Diagnosis is based on recovery of the characteristic operculate eggs in feces or by duodenal drainage (*Clonorchis* 28 by 16 microns *O felineus* 30 by 11 microns *O viverrini* 26 by 13 microns *Dicrocoelium* 38–45 by 22–30 microns) Care must be exercised not to diagnose as 'positive persons who have eaten sheep livers infected with *Dicrocoelium* Prognosis is good in early light infections poor in heavy or chronic infections There is no eminently satisfactory anthelmintic for any of these infections Prevention consists in thoroughly cooking all fresh water fish (*Clonorchis Opisthorchis*) and greens obtained from moist meadows (*Dicrocoelium*) in endemic foci

Ernest Carroll Faust

PULMONARY DISTOMIASIS

Pulmonary distomiasis is produced by the lung fluke *Paragonimus westermani* a moderately small (7 5–12 by 4–6 by 3.5–5 mm) thick, ovoidal worm which most typically lives in little encapsulated pockets that open into the bronchioles and are almost invariably provided with small blood vessels The infection has a wide distribution in the Far East (Japan Korea, China Formosa French Indo China, Philippines, Siam Malaya portions of India) New Guinea Java Sumatra, parts of Africa (Cameroons Congo Tripoli) Venezuela and possibly Peru and the Matto Grosso area of Brazil

Life History—Eggs (golden brown in color operculate measuring 80–118 by 48–60 microns) are laid by the parent worms into the adventitious capsular pockets and are usually discharged into the bronchiole frequently with flecks of hemorrhaged blood and cellular debris They are coughed up and discharged in sputum or swallowed and evacuated with the feces They embryonate and hatch in fresh water and the miracidial larvae enter appropriate snails After sojourn and two fold multiplication in the snail the emerging cercariae enter the soft tissues of fresh water crabs or crayfishes in which they encyst Man and other crab eating mammals acquire infection from consuming uncooked crab or crayfish meat

Morbid Anatomy—The encysted larvae in the small bowel bore through the intestinal wall traverse the peritoneal cavity bore through the diaphragm and enter the lungs eventually reaching sites near the smaller air passages where they settle down and develop into adults Some of the migrating larvae get sidetracked in the abdomen others in the thorax still others get into the cranium and may wander into the brain or its envelopes The lesions produced (Musgrave 1907) consist of (1) abscesses around eggs infiltrated in host tissue (2) pseudotubercles developed around eggs (3) suppurative and (4) ulcerative processes In the lungs the pathologic picture may consist of generalized or localized diffuse cirrhosis cystic dilatation of the bronchi pneumonitis and tubercle like abscesses with accompanying painful cough and hemoptysis Physical signs may suggest bronchopneumonia or pleural effusion The abdominal

where they become lodged Meanwhile the passage of portal blood through the liver becomes increasingly embarrassed, with compensatory passive and active congestion of the spleen leading to tremendous splenomegaly

Symptomatically there is recurrent daily fever epigastric pain with acute tenderness of the abdominal viscera enlarged tender liver and spleen, and loss of appetite and weight Such an acute episode may terminate in a few weeks but is exacerbated with exercise The blood picture at the initiation of the acute stage is one of leukocytosis with intense eosinophilia later it gradually changes to a leukopenia, with secondary anemia although the eosinophilia remains a prominent feature As the *chronic stage* supersedes the acute period weakness skin pallor and dyspnea on slight exertion become conspicuous Digestion is poor emaciation is evident and the superficial veins of the abdomen and thorax become dilated Depending on the degree of hepatic cirrhosis due to closure of portal radicles by eggs ascites may be a prominent feature Digestion of food now becomes negligible as the intestinal wall becomes thickened and its lumen greatly reduced by cicatricial tissue and papillomata This stage may be prolonged for years or the patient may die of pneumonia or other supervening infectious diseases

On the whole schistosomiasis japonica is a more rapidly developing and fatally terminating infection than schistosomiasis mansoni due to the larger number of eggs layed per female per day and the greater percentage of eggs which reaches the liver and sets up periportal tissue changes Moreover ileitis is more conspicuous in the former infection colitis in the latter In both infections however the average case seen by the physician presents a complex picture of early and late stages due to repeated exposure

Diagnosis in these infections is based specifically on the recovery of the eggs of the respective species in feces In the acute stage these appear in the dysenteric exudate or in flecks of blood and mucus attached to formed or semiformed feces In the chronic stage fewer eggs are discharged and require concentration of the stool for their recovery Repeated sedimentation of a considerable amount of stool after dilution in ten parts of water allows the eggs to settle to the bottom of a cylinder jar or large urinalysis glass so that they may be picked up with a pipette Eggs of *S japonicum* are broadly ovoidal measure 70–100 by 50–65 microns have a moderately thick straw-colored shell to which cellular debris is attached and usually have a motile larva inside Those of *S mansoni* are elongated-ovoidal with a conspicuous lateral spine measure 114–175 by 45–68 microns and are less likely to have cellular elements sticking to the shell surface The history of intestinal and visceral involvement with splenomegaly hepatic cirrhosis with ascites and eosinophilia is suggestive of schistosomiasis although Banti s syndrome must be ruled out

Prognosis is good only in acute and early chronic stages provided adequate specific treatment is carried out

Treatment consists in the administration of antimony preferably fuadin (neoantimosan) intramuscularly in a 6 or 7 per cent solution as follows first day 1.5 cc second day 3.5 cc and beginning with the third day 5 cc every alternate day through the seventeenth (total dosage 40 cc) Frequently several courses of treatment may be required This type of administration is superior to the older tartar emetic or sodium antimony tartrate which requires intravenous administration and usually irritates the bronchial epithelium and results in paroxysms of coughing

Prevention consists in avoiding contact with infected water In localized endemic foci bodies of water may be treated with copper sulfate (1 50 000) to kill the snail intermediate hosts Ultimately control will require that feces of infected persons be mechanically or chemically sterilized with respect to the schistosome eggs before the sewage is discharged into bodies of water in which the appropriate snails develop

ERNEST CARROLL FAUST

VESICAL SCHISTOSOMIASIS

(*Bilharziasis*)

This type of schistosomiasis is commonly due to *S haematobium* rarely to *S mansoni* The pathology and the symptomat

skin exposure the adolescent worms are sufficiently strong to migrate against portal blood out to the mesenteric and vesical venules *Schistosoma japonicum* typically migrates to the superior mesenteric venules draining the small bowel *S mansoni* migrates to the venules draining the large bowel (*i e* colic branch of the superior mesenteric vein and the inferior mesenteric vein) *S haematobium* through the inferior mesenteric vessels and *via* the hemorrhoidals or pudendals into the vesical or pelvic veins The distance of the ultimate habitat of the adult worms from the intrahepatic portal vessels is directly related to the incubation times in *S japonicum* 4 to 5 weeks in *S mansoni* 6 to 7 weeks in *S haematobium* 10 to 12 weeks At the end of the incubation period the worms have matured mated and are beginning to lay eggs

Endemic Regions—Schistosomiasis japonica produced by *S japonicum* has a widespread distribution in the Orient including five small foci in Japan one in Formosa extensive areas throughout the river valleys, lakes and irrigation systems of Central and South China, three or four foci in the Philippines and at least one in Celebes Tens of millions of people in these countries are yearly exposed to infection Schistosomiasis mansoni produced by *S mansoni* has an extensive distribution in Egypt, East, Central and West Africa and in many countries of the West Indies and Northern South America including especially Puerto Rico Venezuela Dutch Guiana and large areas on the northern and eastern coast of Brazil Schistosomiasis haematobia (vesical schistosomiasis bilharziasis) produced by *S haematobium* is common throughout the continent of Africa has been reported from the southern tip of Portugal and is prevalent in Syria Palestine and Iraq

ERNEST CARROLL FAUST

INTESTINAL AND VISCERAL SCHISTOSOMIASIS

These types of schistosomiasis are due to *Schistosoma japonicum* and *S mansoni* and on rare occasions constitute a minor part of the clinical picture produced by *S haematobium*

Clinical Course—The disease may be divided into three stages (1) incubation (2) acute (3) chronic The *incubation period* is initiated by the boring of the cercariae into the skin This rarely causes any considerable degree of trauma or cellular infiltration but is accompanied by a needle like pricking pain at each site of entry While the larvae are squeezing their way through the pulmonary capillaries they frequently rupture the delicate blood vessels and set up an acute cellular reaction at each site with a characteristic infiltration of neutrophils and eosinophils occasionally epithelioid and giant cells Considerable numbers of larvae passing through the lungs may occasion an atypical pneumonia Several days later, after the larvae have reached the portal blood and have begun to feed or have been filtered out elsewhere as foreign proteins there is typically a giant urticaria (especially in white patients) attributed to allergic reaction to the parasites Towards the end of the incubation period the liver becomes enlarged and intensely painful there is indication of generalized intoxication late afternoon temperature and night sweats The final prodromal symptom is a toxic diarrhea

With the initiation of egg laying the *acute stage* is ushered in The eggs work their way through the intestinal wall and escape with blood and necrotic tissue cells with associated tenderness of the bowel wall and dysenteric discharge In schistosomiasis japonica the small bowel is at first primarily involved later the colon in schistosomiasis mansoni the large bowel bears the brunt of the damage Soon many of the eggs freed into the perivascular tissues are not able to make an immediate escape into the intestinal lumen and become the centers for intense cellular infiltration leading to miliary abscesses The shallow abscesses may open into the intestinal lumen but the deeper ones usually become transformed by invasion of epithelioid cells giant cells and fibroblasts into pseudotubercles Gradually there is increased difficulty in the digestion and absorption of food and more extensive open ulceration of the bowel occurs In addition eggs in constantly increasing numbers are carried in mesenteric venous blood back into the liver, where they escape into the periportal tissues and initiate miliary abscesses which later transform into pseudotubercles at each site

Control.—Schistosome dermatitis is relatively prevalent in some of the glacier lakes of Michigan Wisconsin and Northern Minnesota Similar reports have come from Germany France Wales and the Federated Malay States Summer guests in endemic foci especially children should be warned concerning the dangers of exposure and copper carbonate in the amount of $\frac{3}{10\,000}$ pound per calculated cubic foot of infected water should be distributed in water along the shore every two weeks during the guest season to kill the snails in which the cercariae develop

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CESTODE OR TAPEWORM INFECTIONS

(*Cestodiasis*)

Cestodiasis is an infection with species of *Cestoidea* (tapeworms) The mature worm (*strobila*) consists of a head (*scolex*) the organ of attachment which is provided with suckers and usually with an anterior complement of hooklets, the "neck" situated immediately behind the head which constitutes the region of growth of the tapeworm and a chain of successive segments (*proglottids*) which arise from the distal end of the neck and become larger and more mature sexually as their distance from the "neck" increases Thus the very young proglottids are designated as *immature* those with fully developed sex organs *mature* and those which serve as storage for eggs *in utero* are the *gravid proglottids* Each mature proglottid is a complete hermaphroditic reproductive unit sexually comparable to a complete trematode The mature egg of human tapeworms contains an embryo within its shell designated as an *onchosphere or hexacanth embryo* Following the onchosphere stage there are one or more larval stages before the worm is ready to develop into the mature strobila Most tapeworms require two or three hosts for the completion of their life cycles

Human tapeworm infections consist of two types

(1) those of which the mature strobila is attached to the bowel wall (*i.e* *intestinal cestodiasis*) and

(2) those for which man is an acceptable larval or intermediate host (*visceral and somatic cestodiasis*)

ERNEST CARROLL FAUST

INTESTINAL CESTODIASIS

Altogether there are thirty or more distinct species of tapeworms which produce intestinal infection in man but only six of these are sufficiently common as human parasites to justify consideration here They are as follows *Taenia saginata* (beef tapeworm) *T solium* (pork tapeworm) *Diphyllobothrium latum* (fish tapeworm) *Hymenolepis nana* (dwarf tapeworm) *H diminuta* (rat tapeworm) and *Dipylidium caninum* (dog tapeworm)

Taenia saginata (*Beef Tapeworm*) — This worm is the largest cestode which infects man A complete strobila measures 12 to 15 feet or more in length and consists of about one thousand or two thousand pro

ology are confined primarily to the bladder and pelvic organs, but there may be considerable pulmonary disease resulting from infiltration of eggs *via* the accessory portal system into the perivascular tissues of the lungs

Clinical Course—The *incubation period* resembles that of intestinal schistosomiasis except that it is more prolonged and never has toxic diarrhea at its termination The *acute stage* is usually ushered in with the painless passage of blood in the urine about three months or more after exposure For months or years there may be no subjective evidence of the disease but sooner or later there is a burning sensation at the time of micturition and increased desire to urinate together with bladder colic and dull pains in the loins and suprapubic region Cystoscopic examination will reveal an inflammatory hyperplasia of the urethra and lower level of the bladder incipient papillomata and concretions of uric acid and oxalates around eggs in the bladder lumen Eggs which have infiltrated into the prostate cause inflammation and fibrosis of this organ The entire bladder wall now studded with pseudotubercles developing around eggs becomes greatly thickened and superficially gritty to the feel although the greater tissue changes are found in the submucosa and muscular layers of the bladder Frequently an endothelial proliferation of the wall of the blood vessels in the area results in multiple thrombosis

The *chronic stage* of vesical schistosomiasis with tissue proliferation and repair begins while egg deposition and extrusion is under way It is characterized by increasing lodgement of the eggs in nearby tissues with multiple abscess and pseudotubercle formation leading to hyperplasia and fibrosis of the entire bladder wall This is frequently accompanied by invasion of streptococci and staphylococci which greatly complicate the picture Thus a condition of chronic cystitis is reached Cystoscopic examination now becomes difficult bladder calculi develop the urethra may become occluded and an intermittent, frequently uncontrolled discharge of urine blood pus and eggs ensues Pyogenic invaders may extend the lesions to the periurethral or perivascular areas or fistulas may extend into the rectum or scrotum Malignancies of the involved tissues are not infrequent The patient becomes incontinent and usually succumbs to extensive dysfunction of the urinogenital system.

Diagnosis consists in the recovery of eggs from the sediment which settles out at the bottom of a urinalysis glass into which the patient has passed a specimen These eggs of *S haematobium* are elongated-ovoidal with a distinct terminal spine measure 112-170 by 40–70 microns, are pale yellow with a moderately thick wall, house a fully developed motile larva and frequently have cellular debris adherent to the shell

Prognosis is relatively good except in the terminal stage provided specific treatment is administered

Treatment consists in the administration of fuadin (neoantimosan) as recommended for intestinal schistosomiasis (*vide supra*) Prevention is similar to that of the intestinal types except that urine is the source for infection of the appropriate snails

Ernest Carroll Faust

SCHISTOSOME DERMATITIS

The fork tailed larvae (cercariae) of several species of nonhuman blood flukes (schistosomes) have been found capable of penetrating the skin of persons wading or bathing in 'infected fresh water with resulting *schistosome dermatitis*

Symptoms—As the infected' water drains off or evaporates from the victim's skin the cercariae penetrate below the epidermis and for a week or more may remain alive in the deeper skin layers It is even possible on the basis of experimental evidence that in small children these larvae may get through the blood stream to the lungs At the time of skin penetration there is a prickling sensation with macule formation followed by urticarial wheals and modification of the macule into a papule Within a few hours to two to three days later intense pruritus of the involved areas is experienced with a marked edema and transformation of the papule into a pustule Scratching of the itching areas frequently produces sepsis Palliatives as calamine lotion should be applied to the involved skin areas and attempts should be made to prevent secondary bacterial invasion

with four suckers and an anterior circlet of hooklets The distalmost proglottid disintegrates in the small bowel, setting the characteristic eggs free These eggs are nearly spherical measure 30 to 47 microns in diameter have a hyaline outer shell and an inner shell provided with a pair of polar thickenings and polar filaments The presence of these filaments is species diagnostic These eggs when evacuated in human stools require no intermediate host If accidentally taken into the mouth of the same or another human being and then swallowed they hatch and develop to the mature worms although a brief sojourn in the stroma of the intestinal villi is required for the transformation of the six hooked embryo into a larval stage This infection is much more prevalent in children than in adults and tends to be familial or institutional in its distribution Worms morphologically indistinguishable from *H nana* are common parasites of rats and mice but are physiologically distinct Hence human infection is of human origin The infection is cosmopolitan but is especially common in the Southern Appalachian area of the United States

Hymenolepis diminuta (*Rat Tapeworm*) **and Dipylidium caninum** (*Dog Tapeworm*) —These tapeworms are relatively uncommon in man although at least 200 authentic cases of the former and several dozen cases of the latter have been reported from the human host The intermediate hosts for these species are insects frequently fleas ectoparasitic respectively on rats or mice and dogs or cats Human infection results from accidentally ingesting infected intermediate insect hosts

Symptoms —The pathogenicity and symptomatology of tapeworm infections probably do not differ intrinsically with the species of tapeworms involved but depend on several factors including the number and mass of the worms trauma and ulceration produced at the sites of attachment to the wall of the small intestine host reaction to toxic by products of the worms and probably constitutional reactions of the host Except for *H nana* it is common to have only a single tapeworm present in the small bowel However although a fifteen foot *T saginata* may fill a 2 liter container many adult patients who harbor such a parasite have no subjective symptoms resulting from the infection On the other hand some persons are extremely sensitive to the presence of a single *H nana*

Clinical Course —An average history of a patient harboring *T saginata* or *T solium* or *Diphyllobothrium latum* is as follows Towards the end of the three month incubation period following the consumption of essentially raw beef or pork or fresh water fish there are a toxic diarrhea and false hunger pains at times systemic toxemia During the early acute stage there is a moderate leukocytosis with an eosinophilia not in excess of 13 per cent There may be diarrhea alternating with constipation After several weeks the average patient will have no apparent evidence of the infection except the almost daily annoyance of proglottids crawling out of the anus and frequently down the leg There may be a mild microcytic or normocytic anemia later a moderate leukopenia In other patients parasitized by *T saginata* or other intestinal tapeworms there may be abdominal colic with or without diarrhea, anorexia loss of appetite and weight insomnia extreme weakness nervousness convulsions in children pronounced anemia of a normocytic or macrocytic type (especially in *D latum* infection)

Diagnosis consists in recovery of the characteristic gravid proglottids in the feces or migrating out the anus less commonly eggs in the feces (*T saginata T solium D caninum*) recovery of the eggs consistently in the feces (*D latum H nana H diminuta*) Prognosis is usually good especially with specific treatment

Treatment —There are several anthelmintics which have been used with success for the evacuation of intestinal tapeworms The writer s experience favors the oleoresin of *Dryopteris* (*Aspidium filix-mas*) Routine treatment involves semi starvation the day before treatment and before going to bed that night taking one ounce (30 cc) of Glauber salts dissolved in a glass of water On the morning of treatment the patient remains in bed takes no food or drink except water (or black coffee) and at 7 00 a m 7 30 a m and 8 00 a m each takes 20 minims of fresh oleoresin aspidii in cap

glottids The "head' is small quadrate-rhomboidal, possesses four deeply excavated suckers but lacks an anterior circlet of hooklets The neck" region is delicate, narrow, and measures a centimeter or more in length Immature and mature proglottids constitute approximately the proximal half of the strobila the gravid ones make up the distal half The uterus of the gravid proglottid consists of a long median longitudinal tube with fifteen to twenty one (usually eighteen) main lateral rami on each side of the main stem Each uterus contains myriads of characteristic eggs each consisting of a walnut colored hull like spherical shell 31 to 43 microns in diameter, and inside the six hooked embryo While eggs of this worm are at times shed inside the human bowel usually the distalmost gravid proglottids, singly or in chains break off from the parent worm and are passed in feces or actively migrate out the bowel Cattle the only known intermediate host pick up the eggs when grazing on moist pastureland contaminated with human sewage The embryos hatch in the ox's small bowel migrate to striated muscle and in three months metamorphose into the mature bladder worm larvae (*Cysticercus bovis*) When man consumes this infected meat inadequately cooked he acquires the infection which requires about three months for incubation This infection is prevalent throughout countries where individuals eat essentially raw beef

Taenia solium (*Pork Tapeworm*) —This tapeworm resembles *T saginata* with the following exceptions It seldom reaches ten feet in length and consists of less than one thousand proglottids The head is armed with a circlet of hooklets anterior to the suckers the 'neck is relatively short and stout the gravid proglottids have a uterus with only seven to thirteen (usually nine) main lateral rami on each side of the main stem The eggs however are indistinguishable from those of *T saginata* and usually escape from the human body in unbroken gravid proglottids Hogs which feed on human feces become infected and within three months the bladder worm larva or pork measle (*Cysticercus cellulosae*) is fully developed in their striated muscle Man becomes infected from eating inadequately cooked pork This infection is uncommon in the United States but is common in Eastern and Southeastern Europe and in many countries of Asia

Diphyllobothrium latum (*Fish Tapeworm*) —This tapeworm is unlike any other common tapeworm of man in many respects It has a narrow spatulate 'head' which is provided only with a pair of longitudinal grooves or sulci for purpose of attachment The strobila may reach several feet in length but never develops strictly gravid proglottids In each mature proglottid there is a patent uterine pore through which immature eggs are discharged soon after they are produced These eggs are therefore always recoverable from feces They are broadly ovoidal measure about 70 by 45 microns are straw colored and possess an operculum at one end When infected human stools are discharged into bodies of fresh water the eggs mature the operculum of each egg opens and ciliated six hooked embryos escape into the water If these swimming embryos are eaten by 'water fleas (*Diaptomus* or *Cyclops*) they develop to the first larval stage in the hemocelic cavity of the water flea' When fresh water fishes eat the infected fleas they become infected with the second larval stage which matures in the flesh of the fish The infection is now ready for man if he eats infected raw fish However the fishes which commonly ingest 'water fleas are usually too small for human food but when these smaller fishes are eaten by larger game fish, the flesh of the latter constitutes the source of human infection *D latum* infection is mostly if not exclusively confined to the North Temperate Zone It is common in Northern Central and Southeastern Europe in many parts of the U S S R Japan the lake districts of Central South Canada and the northern portions of Minnesota and Michigan In the Western Hemisphere it is particularly prevalent in Scandinavian peoples and in Polish Jews Iced fish which is shipped from endemic foci to many urban centers in the United States has provided the source for numerous infections

Hymenolepis nana (*Dwarf Tapeworm*) —This is a minute worm only a few centimeters long and is correspondingly small in other dimensions Its head is provided

or its envelopes cysticerci provoke critical lesions which interfere with important functional processes Possibly little damage may result in these foci until the larvae begin to die whereupon there is an intense cellular infiltration in the area at first inflammatory in nature later fibroblastic in an attempt to wall off the toxic process Thus the tumor mass is appreciably increased The most common site for these damaging lesions is within the brain tissues provoking a Jacksonian type of epilepsy Moreover there is cumulative evidence indicating that persons with subcutaneous or muscular cysticercosis usually develop epileptiform seizures as a result of brain lesions

Treatment —There is no satisfactory treatment for most of these brain cases although occasionally it is possible to remove the intracranial tumor Meticulous personal hygiene is indicated in areas where *Taenia solium* is prevalent

Coenurosis —Related to cysticercosis is the rather rare condition of coenurosis infection with the larval stage of certain tapeworms of the genus *Multiceps* Usually the larvae develop in sheep hogs or rabbits occasionally in man

ERNEST CARROLL FAUST

ECHINOCOCCOSIS

(*Hydatid Disease*)

Echinococcosis or hydatid disease is caused by the larval stage (*i e* hydatid cyst) of the tapeworm *Echinococcus granulosus* of which the dog is the common definitive host and sheep hogs cattle and man the most usual intermediate host

Life History and Morbid Anatomy —The mature worm is a minute organism only a few millimeters long and consists typically of a head a neck a single immature a single mature and a single gravid proglottid The worms live attached to villi or in the glandular crypts of the small intestine The gravid proglottid disintegrates setting *Taenia* like eggs free in the bowel s lumen so that they are evacuated in dog s feces Whenever these eggs contaminate food or drink or otherwise get into the mouth of a susceptible mammal and are swallowed they hatch in the duodenum and the six hooked embryos gain entrance to the bowel wall They reach the mesenteric venules or lymphatics and are filtered out in various foci

In man 70 per cent of the organisms lodge in the liver increasingly smaller percentages in the lungs osseous tissues brain and other tissues of the body On reaching the site where they are filtered out the six hooked embryos transform slowly into minute vacuolated cysts then as they gradually increase in size they are found to have an inner germinative membrane an outer laminated layer and usually a fibrous adventitious capsule The cystic cavity is filled with hydatid fluid The size of the cyst is limited only by its physical and mechanical confines Thus in five years or more an hepatic hydatid cyst may average from 5 to 25 cm in diameter From the germinative membrane multiple scolices or heads (*hydatid sand*) are produced and set free into the fluid filled cavity These scolices vacuolate and develop into daughter cysts Such a mother cyst is viable and is termed *unilocular*

At times the original implantation of the hexacanth embryo is in a site mechanically incompatible with unilocular growth Scolices from the germinative membrane then migrate through the laminated layer and reach the unconfined host tissue through which they multiply and metastasize as *alveolar hydatids* If the scolices reach the spongy tissue of bones the organism develops as a syncytium eroding its way as an *osseous hydatid*

Endemic Regions —Echinococcosis is widely distributed over the face of the earth but is particularly prevalent in sheep raising countries Human infection has an extensive distribution in Central Southern and Eastern Europe the Near East the U S S R China and Japan the North Coast of Africa and South Africa However the disease is of greatest human importance today in Australia New Zealand Argentina and Uruguay in which countries it is a major public health problem In the United States there were previously many case reports of hydatid cyst mostly from immigrants from Eastern Europe Today the number is diminished but several native-born patients are diagnosed each year and

sules or on a spoon with sugar At 10 a m Glauber salts purgation is repeated No food is allowed until copious post treatment bowel movements have been obtained All stools passed for a period of at least twenty-four hours after medication are examined for the 'head' of the worm Unless the 'head is recovered there is no proof that the worm has been eradicated and the "head" may (and usually does) develop a complete new worm in three to four months

Two valuable *alternative methods* of administering oleoresin aspidii are as follows To 4 cc (60 minims) fresh oleoresin aspidii add 30 cc (one ounce) mucilage of acacia and 30 cc (one ounce) sat sol Glauber salts Either administer this emulsion by mouth or by transduodenal intubation to the patient prepared by pre treatment purgation For this method of procedure no post treatment purgation is required

Some physicians prefer *carbon tetrachloride* for removal of intestinal tapeworms The drug is given in capsules in the amount of 3 cc (45 minims) at one administration in the morning with pretreatment fasting and post treatment, precautionary measures as outlined above Although very efficacious this anthelmintic is probably somewhat more toxic than oleoresin aspidii However, the main criticism of its use is its destructive action on the entire tapeworm making it almost impossible from examination of the post treatment stools to discover if the 'head has been evacuated

For children harboring the dwarf tapeworm (*Hymenolepis nana*) it may be advisable to try caprokol (hexylresorcinol crystoids) before utilizing the more toxic specifics Pretreatment Glauber salts purgation is indicated the night before treatment In the morning in a single dose on an empty stomach caprokol is administered in hard gelatin capsules as follows for children of preschool age 0 4 Gm (6 grains) for children six to ten years 0 6 to 0 8 Gm (10–12 grains), for those over ten years the adult dosage of 1 0 Gm (15 grains) Glauber salts purgation is recommended two hours later and food is proscribed for four to five hours

ERNEST CARROLL FAUST

VISCERAL AND SOMATIC CESTODIASIS

Under this group of diseases are included cysticercosis, echinococcosis (hydatid disease) and sparganosis

ERNEST CARROLL FAUST

CYSTICERCOSIS

Cysticercosis is infection with the larval or bladder worm stage of a species of *Taenia* There are on record only two cases of cysticercosis of man referable to the beef tapeworm *T saginata* in contrast there are thousands of published clinical and necropsy reports of human cysticercosis cellulosae (due to the pork tapeworm *T solium*)

Life History —There is thus overwhelming evidence that man is an acceptable intermediate host of *T solium* as well as the only known definitive host of this worm. How then does man become infected? There are three possible methods (1) he may accidentally take into his mouth and swallow the eggs of *T solium* passed in the stools of someone else harboring the intestinal worm (2) he himself may harbor the intestinal worm and by anus to mouth contamination may ingest the eggs (3) he himself may harbor the intestinal worm and by regurgitation eggs discharged from gravid proglottids may be carried up into his stomach then returned to his duodenum Whichever the method is by which the eggs reach the upper levels of the human small bowel they will hatch and the six hooked embryos migrate through the bowel wall into the mesenteric venules or lymphatics They are then carried to all tissues of the body where they lodge and develop into cysticerci within three months Unlike the situation in the pig where essentially only striated muscles are involved in man the cysticerci can become implanted on and develop in any body tissue including muscle subcutaneous layers the heart valves the orbit and the ventricles tissues or envelopes of the brain

Symptoms and Morbid Anatomy —The presence of a few to hundreds of cysticerci in the subcutaneous tissues and somatic muscles produces only slight inconvenience and is essentially painless On the heart valves in the orbit or in the tissues of the brain

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THE NEMATHELMINTHES

(*Roundworms*)

THE NEMATHELMINTHES include the Class NEMATODA or True Roundworms the Class GORDIACEA and possibly other groups The Class NEMATODA contains all of the Roundworms of special medical importance

NEMATODA (True Roundworms or Nematodes) are elongated frequently cylindroidal invertebrates with a cuticula which may be smooth but is at times provided with spines or hooklets particularly around the mouth There is a complete digestive tract consisting of a buccal cavity muscular esophagus mid gut and rectum In the male the rectum opens into a cloaca in the female directly to the outside through an anal pore The body cavity is not lined with epithelium The excretory system lacks any evidence of cilia The sexes are usually separate but syngony (i e male organs in the female worm) occurs in a few species and parthenogenesis in a few others The sex organs are greatly elaborated and occupy the major part of the body cavity Most nematodes are oviparous but a few are larviparous (i e *Trichinella spiralis*) Some eggs are fully embryonated when laved others require a period of incubation outside the human body Some eggs hatch in the soil grow and metamorphose into infective stage larvae Some nematodes require an intermediate host for completion of their larval development Filaria worms are taken up as prelarval *microfilariae* from the peripheral blood vessels or tissues of man by a blood sucking insect in which host they transform into larvae that become infective and are then introduced into or onto the human skin when the insect takes its next blood meal from man Man acquires most nematode infections by the oral route but hookworm and *Strongyloides* larvae actively invade the skin and filaria larvae gain entrance into the skin after escape from their blood sucking insect hosts

The following important nematode infections of man will be considered here trichinosis trichocephaliasis strongyloidiasis creeping eruption ascariasis oxyuriasis filariasis and dracunculosis (For hookworm disease *vide* p 423)

ERNEST CARROLL FAUST

TRICHINOSIS

(*Trichiniasis*)

Trichinosis is produced by *Trichinella spiralis* the trichina worm

Life History —These parasites gain entry to the human body when raw or inadequately cooked pork (rarely bear meat) containing the encysted larvae is eaten most commonly in the form of sausage Excystation of the larvae takes place in the stomach or duodenum and the larvae immediately enter the superficial part of the mucous membrane of the duodenum or jejunum In three or four days the worms have matured have mated and by the fifth day the female is beginning to discharge living young At first some larvae escape into the lumen of the bowel and are evacuated in the feces but as the females migrate nearer to the muscularis mucosae the larvae in

increasing numbers gain entrance to the mesenteric lymphatics and venules and are carried throughout the body, finally settling down in skeletal muscle, where they soon become encysted In the human body this ends their life cycle although they may remain viable for many years In the reservoir host as the hog the encysted larvae constitute the source of infection for the next host Thus in nature a susceptible host harbors all stages in the life cycle of the worm but the infection cannot be propagated unless infected flesh of that host is eaten raw by the next host

Endemic Regions —Trichinosis in man is practically world wide in its distribution wherever hogs are eaten as food but it is rare in some tropical countries Its prevalence in the United States has been emphasized in recent years due to increased recognition of its presence and possibly increased incidence in the human population Autopsy examinations and immunologic tests of the living population indicate that the infection is present in man even if inapparent in all areas of the United States which have been investigated At times mild to severe epidemics of clinical grade have developed due to eating heavily parasitized pork

Clinical Course —Pathologically and symptomatically there are three stages in the disease paralleling the three biologic stages of the parasite, namely (1) the stage of invasion (2) the stage of migration of the larvae and (3) the stage of encystation During the first few days when the excysted larvae are migrating into the duodenal and jejunal mucosa they cause considerable trauma and irritation to the mucosal cells with clinical manifestations simulating acute food poisoning such as nausea vomiting and diarrhea There may be a bright macular or papular eruption on the skin With the beginning of larviposition and larval migration and infiltration of the larvae in the muscles excruciatingly painful myositis is initiated and continues for five or six weeks, resulting from inflammatory reaction wherever the larvae pass This acute reaction is particularly evident in the muscles of respiration speech mastication and swallowing while spastic paralysis of the muscles of the extremities is not unusual Edema especially around the eyes nose and temples accompanies this stage A remittent temperature of 40-41° C (104-105 8° F) is characteristic The blood picture shows a hypereosinophilia with leukocytosis Thrombi in the blood vessels of the viscera or extremities, adenitis, encephalitis and meningitis, ocular disturbances deafness and many other functional disturbances indicate the protean character of the lesions With encystation of the larvae the critical stage of intoxication and sequelae to the earlier tissue damage begins There may be cachexia toxic edema or extreme dehydration Nervous disorders may simulate almost every type of hallucination, mania paralysis or hyperactivity, which usually are transitory but may be permanent In severe fatal cases the pulse is at first fast and strong then weak and cyanosis supervenes The patient may succumb to toxemia to a hypertensive myocarditis resulting from the damage produced by trichina larvae migrating through the myocardium to pneumonia peritonitis, pleurisy and especially to acute nephritis

The above picture is that of the heavily infected individual small groups (rarely larger groups) of which give a history of having eaten pork (country or European style sausage) from a single source Most clinical cases are milder and the great majority of patients have infections below the clinical grade This last type probably has eaten raw or inadequately cooked sausage put up in a large packing plant in which meat of one infected hog was pooled with that of many uninfected ones thus greatly diluting the dose

Diagnosis may be suspected in a patient who gives a history of acute food poisoning following the consumption of pork sausage with sequelae of excruciatingly painful muscular rheumatism While larvae may at times be recovered from diarrheic stools or from centrifuged blood samples specific diagnosis is usually not made until encystation has occurred (ten days or more after exposure) Biopsied deltoid biceps or gastrocnemius muscle strips (1-5 Gm) digested for a few hours in artificial gastric juice at 37° C will provide evidence of motile larvae The most valuable laboratory test is the Bachman intradermal reaction (Bachman 1928

Augustine and Theiler 1932) using 1 5 000 to 1 10 000 dilution of antigen)

Prognosis is good in mild infections but poor in heavy infections particularly if there is no eosinophilic reaction

Treatment consists of supportive and palliative measures The bowels should be kept open and alkalinized and in so far as possible normal kidney function should be carefully maintained Sedatives should be utilized during the stage of muscular pain Cardiac and respiratory stimulation may be indicated Sterile physiologic saline infusions may be administered by hypodermoclysis for dehydrated patients

Prevention consists on the one hand of the thorough heating of all pork intended for human consumption unless previously frozen at —15° C (5° F) for twenty days or at —18° C (—0 4° F) for twenty four hours More far reaching is the need for regulations to prevent the feeding of raw garbage (containing infected pork trimmings) to hogs on the farm or in fattening pens together with extermination of rats and mice in hog raising areas

Ernest Carroll Faust

TRICHOCEPHALIASIS

(*Trichuriasis Whipworm Infection*)

This is an infection with the whipworm *Trichocephalus trichiurus* (syn *Trichuris trichiura*) and involves primarily the cecum and appendix

Life History—The adult worms measure 30 to 50 mm in length have a delicate thread like anterior half and a fleshy posterior half The females have a club shaped posterior extremity the males a flatly spiralled posterior end The anterior end of the worm is inserted or basted into the mucous membrane of the parasitized level of the bowel wall The female lays daily a few thousand bilaterally symmetrical barrel shaped eggs (measuring 50–54 by 22–23 microns), which are usually bile stained and have a blister like plug at each pole These eggs are unembryonated when evacuated in feces On moist shaded warm earth they develop in ten to fourteen days to the infective stage Upon being swallowed they hatch in the duodenum the emerging larvae slowly migrate down to the cecum or appendix become attached and in about three months after ingestion develop to the adult stage The infection is relatively cosmopolitan in all except cold climates but is dependent on moist earth for the extrinsic incubation of the eggs Heavy infections are most frequent in the moist Tropics Children are more commonly exposed than are adults

Symptoms—Mild infections (*i e* with low worm burden) such as usually obtained in the Southern United States seldom produce a distinct train of symptoms even though it has been demonstrated that there is microscopic pathology around the heads of the worms in the bowel wall Nevertheless children are occasionally intolerant of whipworms even in small numbers as indicated by an eosinophilia of 8–25 per cent loss of appetite insomnia nervousness loss of weight urticaria and rarely convulsions In heavy infections (*i.e* several hundred worms) the clinical picture is that of severe hookworm disease Nevertheless the profound secondary anemia of heavy whipworm infection cannot be attributed to mechanical loss of blood from the intestinal mucosa as in hookworm infection and its etiology remains unexplained

Diagnosis of trichocephaliasis depends on the recovery of the characteristic eggs in the feces of the patient Concentration technics as with brine or zinc sulfate centrifugal flotation may be required to apprehend eggs in mild infections Prognosis is good except in heavy infections or those to which children show marked intolerance to the parasite

Treatment with available anthelmintics is not particularly effective Repeated weekly administrations of caprokol by mouth 0 4–1 0 Gm (6–15 grains) on an empty stomach preceded and followed by Glauber salts purgation (1 ounce or 30 Gm in a glass of water) is helpful in evacuating the majority of the worms As an alternative 2–3 cc (30–45 minims) of tetrachlorethylene in 0.5 or 1 cc globules may be prescribed with pre- and post treatment Glauber salts purgation However since effectiveness of these drugs in eradicating whipworms depends on the drug coming in direct contact with the worms in the cecum or appendix pretreatment enemas to wash out these levels of the

bowel is recommended In Central and South America a crude anthelmintic, *leche de higueron* obtained from the trees *Ficus glabrata* and *F doliana*, has specific action on this worm Unfortunately this product ferments readily, its effective fraction "ficin" is unstable and thus far it has not been available for use in the United States

Prevention consists in care not to contaminate food drink or fingers with soil containing embryonated eggs

Ernest Carroll Faust

STRONGYLOIDIASIS

(*Strongyloidosis*)

Strongyloidiasis is produced by *Strongyloides stercoralis*, a delicate roundworm which is of extraordinary interest biologically and epidemiologically because it exhibits capacities for complete parasitic existence on the one hand and complete free living existence on the other

Life History—The adult parasitic worms are primarily parasites of the intestinal tract. The parasitic male when found is tenuously attached to the mucous membrane of the bowel predominantly at the level of the duodenum Usually within a month after arrival at this site the male has been carried down the bowel and evacuated in feces The delicate thread like female measuring about 1 mm in length by 50 to 75 microns in diameter is typically buried in the mucosa of the bowel wall most commonly at the level of the duodenum but heavy infections may extend from the pyloric wall of the stomach to the anus Within the mucous membrane these worms lay partially embryonated eggs resembling those of the hookworms Embryonation is completed in the glands and villi of the bowel and hatching takes place here The escaping first stage (*i e* rhabditoid) larvae burrow out to the lumen of the bowel are passed down and evacuated in feces If the feces are deposited on moist, shaded, sandy humus in a favorably warm climate the rhabditoid larvae feed grow, moult and metamorphose into post feeding *filariform larvae*, which are the infective stage

Morbid Anatomy—On contact with exposed human skin, these larvae penetrate under the epidermis and down to the cutaneous blood capillaries On gaining entry to the afferent blood vessels the organisms are carried through the chambers of the right heart to the lungs They burrow out of the pulmonary capillaries into the air sacs, slowly migrate up the respiratory tree crawl over the epiglottis and are swallowed Meanwhile they have grown in size have become adolescent and by the time they have reached the level of the duodenum have become sexually differentiated If males are present fertilization of the females may occur before they enter the mucosa but there is considerable evidence that the females are able to produce parthenogenetically Within twenty eight days after skin exposure egg laying begins Should larvae be blocked in the air sacs or bronchioles by cellular infiltration the worms continue to grow in these sites and the females may burrow into the bronchial epithelium and establish foci of infection there The above life cycle is the most frequent and is referred to as the *direct mode of development* In favorable warm climates however the rhabditoid larvae evacuated in human stools onto moist ground develop into free living rhabditoid adults which mate lay eggs and continue through one or more free-living generations Eventually, however and usually after one such extrinsic cycle, filariform larvae are produced and the parasitic phase is again established This alternation of parasitic and free living cycles is the *indirect mode of development* A third type of development an insidious and dangerous one for the host is *autoinfection* In some patients usually chronically infected with *Strongyloides* rhabditoid larvae *en transit* down the bowel or lodged in moist feces on the perianal skin become transformed into filariform larvae and are enabled to penetrate the mucous membrane of the intestine or the perianal skin and thus initiate superinfection without having left the host In rare instances rhabditoid larvae metamorphose into filariform larvae without leaving the intestinal mucosa However in all cases these larvae must make a "lung journey" before they can mature in the intestinal wall Internal autoinfection is called *hyperinfection*

Endemic Regions—Strongyloidiasis is apparently coincident with hookworm infection over the face of the globe being most prevalent in the moist Tropics However the relatively meager data on exact distribution and incidence indicate that strongyloidiasis is limited to a more delicate adjustment of extrinsic conditions There are no important reservoirs of this infection

Pathology—The pathology produced by *Strongyloides stercoralis* consists of trauma due to the slow migration of the parasitic female in the intestinal mucosa the escape of eggs into the glands and stroma and the burrowing of hatched rhabditoid larvae Typically the damage involves only the mucosa and does not extend into the submucosa At times cellular encapsulation of adults eggs and larvae occurs but the usual cellular reaction is an infiltration of polymorphonuclear and eosinophilic leukocytes around the worms Irritation of the mucosal cells causes a mucositis and from time to time little patches of necrotic mucosa are sloughed off leaving denuded areas If the infection is extensive there is a mucous watery diarrhea which may alternate with constipation and be reactivated at times of dietary indiscretions or overexertion In heavy infections dehydration may be extreme

Symptoms—Epigastric pain is the most common subjective symptom There is a hypereosinophilia (up to 40 per cent or more) with leukocytosis during the acute stage followed by a leukopenia with a somewhat reduced eosinophilia As the chronic stage develops the fecundity of the female worms may decrease or the worms may become partially encapsulated so that larvae are fewer in the stools and more difficult to discover Meanwhile the patient tends to become toxic, develops dull headaches and periods of despondency Although the parasitic females possibly live for only a year or two the infection may be perpetuated by autoinfection Patients who have been studied by the writer over more than ten years have had persistent infection in spite of the impossibility of a new external source of inoculation *Strongyloides* pneumonitis may also complicate the picture

Diagnosis consists in the discovery of typical rhabditoid larvae occasionally filariform larvae usually in loose or diarrheic stools at times coughed up in sputum These must be differentiated from similar stages of hookworm which may develop in feces left standing in the diagnostic laboratory Hypereosinophilia with a history of diarrhea is relatively pathognomonic The prognosis is fair to good in mild early cases given the benefit of specific therapy poor to grave in severe cases left untreated Absence of eosinophilia is a poor prognostic sign

Treatment consists in the adequate administration of gentian violet medicinal first advocated in the United States by the writer in 1930 For the average adult case one grain (0 06 Gm) is given with meals three times daily (two 0.5 grain Seal Ins or Enseals 1½ hr coating) until 50 grains have been taken One or two such courses of treatment produce cure in about 90 per cent of *Strongyloides* patients For refractive cases and those which develop intestinal colic from taking the enteric coated tablets transduodenal intubation of 25 cc of a 1 per cent solution of the drug is quite effective The rationale of treatment consists of the deep staining of the mucous membrane of the intestine particularly that of the duodenum (hence 1½ hr coating) down to the muscularis mucosae to reach all of the worms Sometime during the administration of the enteric coated tablets and following transduodenal intubation nausea and vomiting may be expected If pulmonary strongyloidiasis occurs intravenous injection of 0.5 per cent solution of filtered gentian violet medicinal may be given to hospitalized patients in amounts not to exceed 20 cc each every alternate day for one month

Prevention consists in care not to walk bare-footed or otherwise expose the skin to polluted soil in the sanitary disposal of human feces and in adequate treatment of detected cases until they have been cured

ERNEST CARROLL FAUST

CREEPING ERUPTION

Creeping eruption is a dermatitis produced by invasion into the deeper layers of the skin by nematode or fly larvae which continue to migrate for weeks or months through serpiginous tunnels in the stratum

germinativum The etiologic agent has in years past been referred to as larva migrans" Among the nematode larvae the hookworm *Ancylostoma braziliense* is most commonly incriminated Filariform larvae of canine and feline strains of *A braziliense* unlike human strains of this species or the other human hookworms on contact with human skin are unable to negotiate an entry into the cutaneous blood vessels However, they progress intracutaneously at the rate of several millimeter to a few centimeters per day producing an inflamed elevated tunnel which becomes vesicular and frequently is complicated by invasion of pathogenic bacteria There is an intense pruritus of the involved area almost invariably provoking scratching This infection is distributed throughout the coastal areas of the Southeastern and Gulf States especially in Florida but occurs elsewhere in warm climates The foot is most frequently involved but any other area of the skin which comes in contact with moist sandy soil where *A braziliense* infected dogs or cats have previously defecated is readily subject to infection

Another nematode whose larvae cause creeping eruption is *Gnathostoma spinigerum* with a distribution in the Orient and the South Pacific The lesions of gnathostomiasis may be similar to those described for *A braziliense* or may be more like cutaneous abscesses

Creeping eruption produced by fly larvae (*i e maggots*) is a dermal myiasis and is due primarily to skin invasion by maggots of the horse bot *Gasterophilus* Eggs are layed on the human skin hatch and the maggots penetrate down to the stratum germinativum or corium then travel in this layer for weeks or months like *A braziliense* larvae Differential diagnosis can readily be made by massaging the involved site with clear machine oil If numerous black bands (of spines) are seen with a hand lens the agent is *Gasterophilus*, otherwise most likely it is *A braziliense* Prognosis is good if septicemia is avoided

Treatment —Recommended treatment for *A braziliense* creeping eruption is the application of ethyl chloride spray to freeze the site at the inner end of the tunnel where the larva resides, for *Gasterophilus* it consists of removing the larva with a sterile sharp needle, and dressing the wound with mild antiseptic bandages

Prevention —Control of creeping eruption of hookworm origin consists of avoiding skin contact with sites where dogs or cats have defecated For *Gasterophilus* intensive campaigns to eliminate horse flies should be instituted

ERNEST CARROLL FAUST

ASCARIASIS

Ascariasis is produced by the large roundworm *Ascaris lumbricoides*, which inhabits the lumen of the small bowel The worm is elongate cylindroidal, and tapers bluntly at the anterior end and to a moderately sharp point posteriorly The head is provided with three conspicuous fleshy lips surrounding the triangular mouth The males average 15 to 31 cm in length by 2 to 4 mm in diameter the females 20 to 35 cm by 3 to 6 mm The male is curved ventrally at the posterior extremity

Life History —Females lay up to 200 000 eggs each per day These may be infertile or fertile The former are more elongated and have a disorganized mass of granules and globules completely filling the inner shell The fertile eggs are broadly ovoidal measure 45–75 by 35–50 microns have a spherical heavily granular unsegmented egg cell a thick hyaline inner shell and a thick mammillated usually bile stained outer shell When evacuated in human feces onto the ground they proceed to embryonate and in nine days or more will contain a motile rhabditoid larva coiled inside In another week this unhatched larva sheds its cuticle and now becomes infective It remains infective for months and possibly years Only direct sun s rays or heat will kill the embryonating or infective stage egg When human beings pick up these mature eggs on their fingers or otherwise get them into their mouths and swallow them the eggs hatch in the duodenum or jejunum and the emergent larvae enter the intestinal wall and make their way to the lungs *via* the mesenteric lymphatics or venules vena cava right heart and pulmonary arteries They break

out of the pulmonary capillaries into the air sacs, migrate up the respiratory tree crawl over the epiglottis are swallowed and in sixty five or seventy five days after exposure become adult worms in the lumen of the small intestine

Endemic Regions —Ascariasis is cosmopolitan in its distribution but is more prevalent in warm than in cold climates Its epidemiology differs materially from that of hookworm disease or oxyuriasis The soil is seeded with *Ascaris* eggs passed in feces of infected individuals Primarily this is the result of promiscuous defecation by small children in and around the home (Cort 1931) These same children and their associates later on become exposed to new infections when they pick up eggs that have become fully embryonated Thus infection in an environment tends to become endemic and infected individuals may at one and the same time harbor adult egg laying *Ascaris* and young worms in the intestine as well as larvae *en route* through the lungs

Morbid Anatomy —The first important lesions produced in ascariasis are in the lungs due to the breaking out of the migrating larvae from the pulmonary capillaries into the air sacs These rhabditoid larvae are considerably more robust than the migrating filariform larvae of hookworms and *Strongyloides* and produce more trauma and hemorrhage In considerable numbers they cause small pools of extravasated blood to accumulate in the air sacs provoking polymorphonuclear infiltration and resulting in an atypical lobular pneumonia which constitutes a distinct clinical entity *Ascaris pneumonia* especially in small children In the small bowel adolescent and adult ascarids may produce no apparent disturbance even when present in moderate numbers In the absence of reinfection the worms will be passed spontaneously or die within the bowel in approximately a year s time Digestive upsets or other abnormal conditions within the bowel will frequently irritate these worms and provoke activities hazardous to the patient They may be regurgitated and vomited or escape through the external nares they may block the common bile duct or the appendiceal lumen setting up acute inflammatory processes or may perforate the intestinal wall and initiate peritonitis The most common complaint in *Ascaris* patients is intestinal colic Rarely the worms have been found in the parenchyma of the liver and in the pleural cavity Not infrequently in small children knotted masses of worms produce acute obstruction of the bowel and require immediate surgical intervention Even when the worms cause little or no traumatic damage the by products of living or dead worms may produce marked toxic manifestations as edema of the face and giant urticaria, accompanied by insomnia loss of appetite and weight extreme nervousness and in extreme cases cachexia Moreover it has been convincingly demonstrated that *Ascaris* children like hookworm children are mentally retarded A moderate eosinophilia may be expected in ascariasis otherwise the blood picture is not materially altered

Diagnosis is made by the recovery of the eggs of *Ascaris lumbricoides* in human feces Usually fertile eggs will be found but where female worms alone are present only infertile eggs will be found In about 5 per cent of infections only males are present and diagnosis must be tentatively based on symptoms until a therapeutic test has been made In most infections technics for concentration of the eggs from feces are unnecessary to provide specific diagnosis due to the large number of eggs discharged daily by each female worm The spontaneous passage of one or more worms by anus or mouth does not necessarily mean that additional worms are present This can be verified by stool examination two or three days after the worms have been evacuated

Prognosis is good except in patients where obstruction or grave traumatic injury has been produced by the worms

Treatment is best accomplished by the administration of caprokol (hexylresorcinol crystoids) which has a 90–95 per cent worm removal rate for *Ascaris* Following pretreatment purgation the night before with one ounce (30 Gm) of Glauber salts dissolved in a glass of water the drug is administered in one dose in the morning on an empty stomach in hard gelatin capsules of 0 1 or 0 2 Gm size For children of pre-school age the dosage is 0 4 to 0 6 Gm (6 to 9 gr) for children from 6 to 10 years 0 8 Gm (12 gr) for older children and adults 1 0 Gm

(15 gr) The patient is required to swallow the capsules without chewing them to prevent superficial irritation of the buccal mucosa Food is proscribed for four to five hours and a post treatment purge of Glauber salts is given two hours after the drug to evacuate dead and dying worms as soon as possible and thus prevent absorption of their toxic products An alternative prescription which is valuable in combined infections of *Ascaris* with *hookworms* or *Trichocephalus* is the following tetrachlorethylene 2 7 cc (40 minims) oleum chenopodii 0.3 cc (5 minims) in 0 5 cc capsules or on a teaspoon with sugar Pretreatment Glauber salts purgation the night before administration of the anthelmintic on an empty stomach and post treatment Glauber salts purgation are indicated For children the dosage is 3 minims per year of age up to 15 years

The above prescriptions are eminently satisfactory for intestinal ascariasis During migration of *Ascaris* larvae through the lungs and for ectopic infections there is no specific chemotherapeutic procedure Physicians are requested to be *Ascaris* conscious in cases of atypical pneumonias especially in children in *Ascaris* communities

Prevention constitutes an integral part of the protection of human beings against the possible dangers of *Ascaris* infection since successful treatment of individual cases does not prevent reinfection from the same seed beds where infective stage eggs are planted Children must be taught to use sanitary toilets or privies on all occasions and must be warned of the dangers of contaminating fingers candy or play objects with soil Heavily infested ground around the house should either be treated with live steam (70° C for five minutes is lethal for *Ascaris* eggs) or spaded up and the top soil turned under Ascariasis in hogs is not a source of human infection since human and porcine strains are physiologically distinct

ERNEST CARROLL FAUST

ENTEROBIASIS

(Oxyuriasis)

Enterobiasis familiar to most clinicians as oxyuriasis is infection with the pinworm or seatworm *Enterobius vermicularis* The adult worms are small delicate objects (male 2–5 mm by 0 1–0 2 mm female 8–13 mm by 0 3–0 5 mm) and are provided with a pair of ear like lateral flaps or alae in the cervical region The male has a ventrally curved posterior end the female a sharply pointed tail

Life History—These worms live as young adults typically in the cecum and appendix with their heads attached to the mucosa Gravid females become free and migrate in the bowel usually down and out the anus especially at night when the patient retires The worms crawl in a sinuous path on the perianal and perineal skin discharging their eggs *en route* They seldom if ever return to the bowel In female patients the worms may enter the external meatus of the genital tract crawl up to the tubules and migrate into the peritoneal cavity Eggs are layed within the bowel only in about 5 per cent of positive cases and such eggs are usually nonviable Those deposited by thousands outside the anus are practically mature when deposited They are hyaline colorless ovoidal objects with a relatively thick shell usually flattened on one side measuring 50–60 by 20–30 microns and contain a coiled, frequently motile larva

They may produce infection by direct anus to mouth contamination the common method of reinfection or by being distributed by air currents from bed linen pajamas etc onto objects in the bedroom and then getting into the mouth from fingers in contact with contaminated objects Infection is commonest in children especially in large families or in institutions Enterobiasis is also common in mental hospitals The highest incidences of infection occur in large dormitory groups the lowest in families where each individual has his own bedroom The mature eggs upon being swallowed hatch in the small bowel and the emerging larvae migrate slowly down to the levels of the cecum and appendix where they become attached and develop into adults in two months or possibly less

Morbid Anatomy—Pathologic processes are at times developed at the sites where the adult worms reside especially in the tip of the appendix Considerable hemorrhage may occur at the points of attachment while pyogenic organisms invade the aban

doned sites and may initiate inflammatory reactions, at times leading to submucosal abscess formation The clinical picture is that of acute or subacute appendicitis Eosinophilia and leukocytosis may or may not be produced By and large however the principal difficulty produced in enterobiasis is associated with the migration of the gravid females out of the anus and on the perianal and perineal skin and at times causes almost insufferable pruritus This leads to scratching of the area and consequent contamination of fingers Frequently the itching skin becomes inflamed or raw and may require treatment with antiseptic ointment as yellow oxide of mercury Chronic pruritus leads to insomnia nervousness at times hysteria rarely convulsions in small children Nycturia in boys and nymphomania in adolescent girls are complicating states not infrequently observed

Diagnosis based on recovery of eggs of *Enterobius* in feces even by concentration technics is hopelessly inadequate Six or seven consecutive cellophane swab examinations (Sawitz), of the perianal and perineal skin preferably in the morning before the patient bathes or defecates provide a nearly perfect criterion of infection

Prognosis is almost always good especially with adequate treatment

Treatment consists preferably in the administration of gentian violet medicinal in the form of four hour Seal Ins or Enseals coated tablets of ⅙ or ½ grain (0 012 or 0 03 Gm) size For adults a course of treatment consists of one grain (0 06 Gm) three times daily with meals for eight days rest one week then repeat treatment For children the dose is ⅙ grain (0 01 Gm) daily for each year of apparent not actual age This treatment should be given to all infected persons in the family or other environmental group otherwise there will be repeated reinfection With mass therapy as recommended 90 per cent cures may be expected

Prevention has not been successful where only hygienic measures have been carried out On the other hand mass therapy with gentian violet has proved successful in most groups Occasional refractive cases suggest the need of temporary abandonment of the infested habitat since it is unlikely that the eggs remain viable for more than a few weeks Only by persistent efforts can eradication be effected

Ernest Carroll Faust

FILARIASIS

Filariasis is an infection with one or more of several true filaria worms which are thread like and have the following general characteristics and life cycle

Life History —The female worms in their natural habitats in the human body give birth to delicate elongate embryos known as *microfilariae* If the old egg shell remains around the microfilaria it is said to be sheathed if the microfilaria is naked it is unsheathed These microfilariae periodically or constantly migrate through peripheral blood vessels (or through cutaneous tissues) from which they are taken up by appropriate species of blood sucking flies Within the fly the microfilariae migrate from the lumen of the stomach' to the thoracic muscles where they metamorphose into sausage shaped first stage larvae These larvae grow metamorphose through several stages and in approximately two weeks or less become motile filariform larvae They now migrate down the proboscis sheath of the fly and at the time of the fly s next blood meal are introduced into or nearby the puncture wound which they make in the human skin These infective stage larvae then migrate from the skin to the sites where the adult worms will eventually mature The incubation period is usually one year or less after which the females of this new generation give birth to a brood of microfilariae

The following table (Table 1) provides information on the human filaria worms which are important either from the point of view of the pathologic changes and symptoms that they produce or from their prevalence over large areas of the world

Bancroft s Filariasis —This filarial infection is produced by *Wuchereria bancrofti* a delicate thread like worm which lives in lymph vessels and lymphoid tissues particularly in the groin and the lymphoid tissues associated with the external genitalia

Life History —Infection is initiated when

the filariform larvae are introduced onto or into the skin by infected mosquitoes especially *Culex fatigans* the tropical house mosquito Nothing is known of the subsequent history of these larvae until they mature into adult worms and the fertilized females begin discharging microfilariae This *incubation period* requires about one year and is usually symptomless This is succeeded by the *patent symptomless period* which continues for months or even years The microfilariae pass from the immediate vicinity of the parent worms into lymph vessels and thence into visceral blood vessels Typically at night (especially between midnight and 2 a m) when the patient relaxes the microfilariae surge through the peripheral circulation but return to the viscera during daytime when the patient is active

Symptoms —Sooner or later however the patient becomes toxic with frontal headache and a feeling of depression These prodromata are followed by the *acute period* with inflammation of the involved superficial lymph vessels which become raised and exquisitely painful, and an associated lymphatic fever After ten days to two weeks the lymphangitis disappears and temporarily the patient returns to a state of well being Recurrence of the inflammatory process may be anticipated usually at periodic intervals and eventually the *chronic period* gradually replaces the acute stage

Morbid Anatomy —The pathologic basis for the acute and chronic stages consists fundamentally in cellular infiltration around the locations where the adult worms are discharging appreciable amounts of toxic by products and particularly when they become moribund later die and become calcified The acute reaction is inflammatory but is gradually replaced by extensive fibrous encapsulation of the parent worms and blockage of lymph channels distal to the worms' locations Fibrosis extends along these channels until elephantiasis with nonpitting edema of the member develops or lymph varix is produced The lower extremities male genitalia and glands of the groin are

TABLE 1 —THE MORE IMPORTANT SPECIES OF TRUE FILARIAL WORMS PARASITIZING MAN

NAME	LOCATION OF ADULT WORM IN HUMAN BODY	CHARACTERISTICS OF MICROFILARIA	INSECT INTERMEDIATE HOST AND TRANSMITTERS	GEOGRAPHICAL DISTRIBUTION
Wuchereria bancrofti (Bancroft s filaria)	Lymph vessels and lymphoid tissues especially in lower trunk and in lower extremities	Sheathed typically with complete nocturnal periodicity in peripheral blood	Species of Mosquitoes especially *Culex fatigans*	Tropics and Subtropics with extensive distribution
Wuchereria malayi (Malay filaria)	Lymph vessels and lymphoid tissues especially in upper trunk and upper extremities	Sheathed with relative nocturnal periodicity in peripheral blood	Species of Mosquitoes especially *Mansonioides* and *Anopheles* spp	Central and South China Indo-China Malaya Dutch East Indies S E India
Acanthocheilonema perstans (Persistent filaria)	Body cavities	Unsheathed without apparent periodicity	Species of *Culicoides*	North Africa coastal South America from Venezuela to Argentina Dutch New Guinea
Mansonella ozzardi (Ozzard s filaria)	Body cavities	Unsheathed without apparent periodicity	Species of *Culicoides*	South America Yucatan West Indies
Onchocerca volvulus (convoluted filaria)	Subcutaneous tissues immobilized in fibrous tumors	Unsheathed migrates through skin not in blood vessels	Species of *Simulium*	Africa Pacific slope of Southern Mexico and Guatemala
Loa loa (loa worm eyeworm)	Subcutaneous tissues migrating	Sheathed with diurnal periodicity in peripheral blood	Species of *Chrysops*	Africa

most frequently involved but the processes may extend into the peritoneal cavity (with chylous ascites) or into the bladder (with chyluria) It is entirely likely that with the almost complete loss of cutaneous blood circulation in the involved member and the consequent cracking of the skin pathogenic bacteria and fungi enter and complicate the picture they may in fact be responsible for initiating recurrent acute attacks of lymphatic fever Nevertheless there is adequate evidence to support the view that the initial lesion is immediately around the adult worms and is of filarial origin

Diagnosis may be accomplished during the patent symptomless period and the acute stage by the recovery at night of the characteristic microfilariae in thick-drop blood films stained with Giemsa stain When the adult worms die the production of microfilariae ceases so that dependence must be placed on gross pathology and x ray evidence of calcified worms in the midst of the lesions Ultimate prognosis is relatively poor due to the amount of fibrous tissue repair

Treatment is not eminently successful There is no specific anthelmintic available Sulfonamides should be used for streptococcic and staphylococcic invaders Surgical procedures include radical operation to remove elephantoid tissues and a modified Kondolean operation for the lower extremity Knott (1938) has used tight Turkish towel bandaging of the involved lower extremity and has reported marked success in reestablishing drainage through collateral lymph channels reduction of the elephantoid tissues and reestablishment of blood circulation in the skin

Prevention of Bancroft s filariasis is a difficult problem It involves fundamentally the clearance of mosquito breeding sites around endemic foci but considerable protection may be temporarily afforded by screening together with the use of pyrethrum sprays and repellants such as Sta way against adult mosquitoes

Filariasis malayi is produced by *Wuchereria malayi* which is closely related to but specifically different from *W bancrofti* The development in the mosquito (*Mansonioides Anopheles* etc) method of inoculation of the human victim incubation period patent symptomless period and the development of the acute and chronic states are much the same as in Bancroft s filariasis except that the lesions occur preponderantly in the upper trunk and upper extremities *Diagnosis* is made in a similar manner The prognosis is usually much better, even without surgical intervention The *clinical aspects* of filariasis malayi have been little studied In Travancore India new infections have been greatly reduced by removing the water plants on which the larval stages of the mosquito *Mansonioides annulifera* live (Sweet and Pillai 1937)

Filaria infections due to *Acanthocheilonema perstans* and *Mansonella ozzardi* have a widespread distribution (see Table 1) but produce no proved pathology or symptoms of clinical grade It is important to recognize the diagnostic characters of their microfilariae so that infections with these worms will not be confused with pathogenic filariae of man

Onchocercosis is produced by *Onchocerca volvulus* which is transmitted by the biting gnat *Simulium* In Africa it has an extensive distribution in the Western Hemisphere its distribution is limited to a narrow strip of coffee growing uplands on the Pacific slope of Guatemala and to the States of Chiapas and Oaxaca possibly elsewhere in Mexico The adult worms live tightly coiled usually in pairs in fibrous subcutaneous tumors which become palpable within a year or less after exposure to the infection They vary in size from a pea to a small orange The tumors may be located on any part of the body In Africa they are found conspicuously at the junctions of long bones in Guatemala and Mexico most of the tumors are on the head especially in the temporal areas and occiput The unsheathed microfilariae escape from the parent tumors and migrate through the skin and subcutaneous tissues frequently accumulating in the corneal conjunctiva tissues of the eye ball or in the optic nerve The parent lesion is usually painless seldom abscesses and causes little functional damage On the other hand the invasion of the microfilariae into the tissues of the eye provokes damaging changes (including inflammation of the iris the ciliary body retina and choroid punctate hemorrhage around the limbus punc

tate vascular or interstitial keratitis of the cornea, and edema of the conjunctiva), leading to photophobia and diminished vision Involvement of the optic nerve leads to complete blindness Moreover inflammation of the tissues in the temporal area may produce an erysipelatoid appearance especially around the ear and on the ear lobes

Diagnosis of onchocercosis may be suspected in patients living in endemic areas or previously exposed there who have one or more characteristic parent tumors especially with evidence of diminished vision Specific diagnosis requires the demonstration of the microfilaria of *O volvulus* obtained from biopsied skin near the tumor or from biopsied corneal conjunctiva, or in the aspirate of the tumor after puncture

Treatment—There is no eminently satisfactory chemotherapeutic The tumors should be removed as soon as they develop to reduce the likelihood of eye damage from microfilarial invasion Plasmochin (0 1 per cent solution) when introduced into the anterior chamber of the eye is believed to arrest ocular symptoms by killing the microfilariae Prevention might be accomplished by cleaning out breeding places of the *Simulium* intermediate hosts but since these locations are usually under stones in mountain streams no practical control has been developed However relatively good results have been demonstrated in endemic foci by enucleation of the parent tumors in patients as soon as they appear

Loaiasis is produced by Loa Loa the so called eyeworm because of its propensity to wander across the front of the cornea during its continual migrations through the peripheral tissues of the body This thread like nematode lives as a mature organism in the subcutaneous tissues but is not immobilized within a fibrous tumor as is *Onchocerca volvulus* It characteristically advances a few centimeters a day in a raised serpentine track and during its wanderings typically reaches the temporal region and passes under the corneal epithelium across the front of one eye the bridge of the nose then the other eye and finally out to the other temple and down the neck to the trunk In its migrations the worm sets up a temporary inflammatory reaction referred to as a fugitive swelling' There is no permament impairment of tissues or organs only the inconvenience and nervous reaction from constant slight irritation The microfilariae are diurnal in their appearance in the peripheral blood stream They are picked up by the mango fly *Chrysops* in which they are transformed into infective stage larvae and are then inoculated again into man The disease is confined to the Continent of Africa but in the United States occasional cases are seen with a history of having lived in endemic foci

Diagnosis is frequently provided by patients who know of the migrations of the parent worms in their peripheral tissues The lesions must not be confused with those of creeping eruption (*vide supra* p 415) The characteristic sheathed microfilariae present in peripheral blood in the daytime provide specific diagnosis

Prognosis is always good

Treatment consists in the skillful extraction with a sharp hooked needle of the parent worm as it migrates under the epithelial layer of the cornea Novocaine anesthesia is not advised since it drives the worm back into inaccessible tissues

Prevention consists in avoiding water courses around which mango flies breed and hover

ERNEST CARROLL FAUST

DRACUNCULOSIS

(Dracontiasis)

Dracunculosis is produced by *Dracunculus medinensis* referred to as the dragon worm Medina worm or Guinea worm This worm superficially resembles the true *filaria* worms but in structure and life cycle is quite different The male worm is a small thread not over 40 mm in length while the female measures 70 to 120 cm in length by 0 9 to 1 7 mm in diameter

Life History—The mature worms live in the viscera or deeper somatic tissues of man and several species of mammals The gravid female migrates to the skin and on arrival produces a cutaneous blister over her anterior extremity When this area comes in contact with fresh water or a goat skin water bag seeps water onto the skin of the carrier s back the blister bursts and the

dragon worm discharges a brood of rhab ditoid larvae into the water These larvae are picked up by little water fleas of the genus *Cyclops* migrate to the hemocelic cavity of the *Cyclops* and mature When man or other susceptible host then swallow raw water containing the infected fleas he acquires the infection which requires about one year for incubation Following this the gravid female migrates to the skin to shed her progeny

Endemic Regions —This infection is highly endemic in extensive areas of India Arabia Persia Afghanistan Turkestan the southeastern states of the U S S R and Africa Autochthonous cases have been re ported from the Dutch East Indies the Guianas and Bahia (Brazil) In the United States and Canada fur bearing mammals and in China dogs may be infected but no native human cases have been reported from these latter countries

Symptoms —During the migration of gravid female dragon worms from the deeper tissues of the body to the skin there is typi cally a pronounced histamine like symptom complex which is readily amenable to epine phrine therapy The subsequent period of weeks during which the female is discharg ing larvae through the skin opening is one subject to invasion of pyogenic bacteria which constitute the greatest hazard of the infection Since time immemorial infected natives have pulled out the worm a centi meter or two a day by coiling it around a small stick which is bound to the site be tween manipulations Attempts to pull the worm out rapidly invariably causes it to break off in its tunnel with suppuration No practical modern aseptic procedure has been developed to supplant the native technic

Diagnosis is usually self made by infected patients who regard the infection as a God sent affliction

Prognosis is good except when septicemia develops

Treatment —There is no satisfactory chemotherapeusis Probably the most practi cal *control measure* consists in placing small fishes in all bodies of fresh water as ponds wells etc in endemic areas to eat the in fected *Cyclops*

The **Gordiacea** or hair worms (hair snakes) have from time to time been re ported as parasites of the digestive tract of man All cases investigated have proved to be ones of temporary parasitism due most likely to ingestion of raw water containing the immature or maturing worms which are temporarily free living following a parasitic phase in grasshoppers and other insects

ERNEST CARROLL FAUST

HOOKWORM DISEASE

(Ancylostomiasis Uncinariasis Tropical Chlorosis Miner s Anemia)

Definition —Hookworm *disease* is a clin ical syndrome caused by infection with *Ancylostoma duodenale* or *Necator americanus* Hookworm *infection* implies the harboring of hookworms in the intestine with or without symptoms

History.—*Ancylostoma duodenale* was discovered by Dubini in Italy in 1843 *Necator americanus* was discovered by Allen J Smith in Texas and by Ashford in Puerto Rico and was named by Stiles in 1902 Clinical hookworm disease was first recognized as such by Perroncito in 1880 in laborers who were constructing the Saint Gotthard tunnel through the Alps Looss in Egypt discovered that the larvae penetrate the skin and in 1904 demonstrated the route of migration of the larvae through the blood and respiratory tract to the intestines

Distribution and Incidence —Hookworm infection is endemic in many parts of the world between 36 degrees north latitude and 30 degrees south latitude Light infections are found in hot dry climates and moist cooler climates where environmental condi tions are favorable Moisture warmth, sandy or loose soil and promiscuous de-fecation are the chief factors responsible for heavy infections A mean monthly tempera ture of 50° F is necessary for the develop-ment of the larvae in the soil Regions hav ing less than forty inches of rainfall a year may show a high incidence of light infections but rarely have heavy infections The dis ease is almost entirely rural except for mines where excreta disposal is unsanitary The occupations in addition to farming and mining which are most often associated with hookworm disease are coffee tea sugar cacao and banana raising in the tropics and mulberry growing associated with the silk worm industry in China and Japan This is

because the people work barefoot in fields fertilized or contaminated with human excreta The two species of hookworms originally had separate areas of distribution, both being limited to the Old World Ancylostoma north of the 20th meridian of north latitude Necator south of this meridian The present distribution is due to the migration of people from the original areas Ancylostoma is present alone in the Mediterranean area parts of India northern China and Japan and in most mines Necator in Central and South Africa and in North and South America The two worms are found together in parts of India southern Asia and parts of Central and South America The hookworm belt in the United States is principally along the Atlantic and Gulf seaboards from North Carolina to eastern Texas The other important area is the southern Appalachian region including southwestern Virginia western North Carolina eastern Kentucky and eastern Tennessee In some tropical areas where hookworm campaigns have not been conducted practically 100 per cent of the rural population are infected Where such campaigns have been conducted and where sanitary disposal of excreta has been introduced a considerable reduction has taken place Studies by Keller and Leathers from 1930 to 1938 in six southern states showed that there had been a reduction in incidence of hookworm infection in the rural white population of these states from 39 per cent to 18 per cent since 1910–1914 when the original survey was made by the Rockefeller Sanitary Commission

The white and brown races are more susceptible than the Negro In infected families the larger the number of infected individuals the greater is the average intensity of infection Incidence and intensity increase with age up to the fifteen to nineteen age group after which there is a gradual decline Males show a higher incidence and intensity than females and the peak comes a little later in life This is undoubtedly due to greater exposure

Etiology —The human hookworms are nematodes (round worms) measuring about 1 cm in length the female being slightly larger than the male Ancylostoma is slightly larger than Necator The anterior end is curved dorsally The buccal cavity is armed with ventral teeth (Ancylostoma) or cutting plates (Necator) The male has a copulatory bursa at the posterior end consisting of finger like rays The worms inhabit the small intestine mainly the jejunum They attach themselves to villi which are sucked into the buccal cavity and they secrete toxic fluid which causes dilatation and rupture of the capillaries and prevents coagulation of the blood The worms feed mainly on blood and lymph pumped into the intestine of the worm by the muscular esophagus The worms are wasteful of this food only fluid constituents being absorbed Most of the ingested material is rapidly excreted through the anus Wells showed that a single dog hookworm could ingest 0 8 cc of blood daily if it fed continuously Although a hemolytic toxin has been demonstrated in extracts of hookworms it has not been shown that such a toxin contributes to the anemia or other symptoms The life span of the hookworm may be several years the heavier the infection the shorter the average life span of individual worms

A female hookworm lays between 6000 and 15 000 eggs per day, Ancylostoma more than Necator The larva develops rapidly in the egg and hatches under favorable conditions of moisture and temperature in about three days The rhabditiform larva ruptures the egg shell and after two moltings within a few days becomes an infective filariform larva enclosed in a transparent sheath This larva may travel upward or downward in the soil for a few inches as changes in moisture require Its life span may be several weeks in moist soil although it does not feed as long as it retains its sheath When the skin of man is exposed to infected soil the larva penetrates rapidly enters a blood vessel and is carried to the lungs where it breaks out into an alveolus It then makes its way up the bronchi and trachea into the pharynx and is swallowed and passes into the small intestine where it develops into an adult About six weeks is required from the time of penetration of the skin until eggs appear in the stools

Clinical symptoms are dependent mainly upon the chronic loss of blood producing a secondary anemia A diet low in iron content as is found among the rural people in

many parts of the world prevents recuperation from the loss of blood sometimes even after the worms have been expelled A vicious cycle consisting of poor nutrition, inability to work and poverty is established in heavy infections and contributes largely to the problem of the disease

Morbid Anatomy —The *blood* in heavily infected persons presents a chlorotic type of secondary anemia in which the average volume of the red blood cells is considerably decreased and the hemoglobin is reduced in greater proportion than the number of erythrocytes A few nucleated red cells may be found In extreme cases a picture of primary anemia may be present but this is probably due to other complicating factors The white blood cells are usually normal in number and proportion except that there is usually an eosinophilia ranging from 5 to 25 per cent The eosinophilia is more prominent in early infections and may be absent in severe cases The *bone marrow* shows an increase of cellular elements and vascularity There is an increase of young hematopoietic cells and a great increase of red cells in the normoblast stage The *spleen* is usually somewhat reduced in size The *liver* may show marked fatty infiltration The *small intestine* in patients dying of the disease usually shows some atrophy of the epithelium and increase in the connective tissue elements of the mucosa This has been interpreted as a possible explanation of the apparent inability of severe hookworm cases to absorb important food elements in normal amounts Petechial hemorrhages are found at the site of attachment of the worms The *heart* is dilated and its muscle flabby There is often edema of the tissues and sometimes even of the brain and free fluid in the serous cavities

Symptoms —*Stage of Invasion* —The larvae in penetrating the skin produce lesions which are called ground itch They consist of maculopapules which become small vesicles These are often confluent and rupture discharging serous fluid They are surrounded by local erythema and swelling Itching is severe The commonest site is on the feet particularly between the toes but in miners may be on the arms legs or buttocks Regional lymph nodes are often enlarged especially if secondary infection takes place

The larvae in passing through the lungs may produce bronchitis if a heavy infection occurs at one time It may be accompanied by fever It has been noted particularly among miners

Symptoms Produced by Adult Worms —Very light infections usually produce no recognized symptoms but elimination of the worms sometimes increases the vigor or accelerates normal development in children Mild cases show slight pallor of the skin with a yellow tinge dryness of the skin with decreased perspiration sometimes slight discomfort in the abdomen slight palpitation of the heart on exertion slight weakness of the muscles and distaste for work The appetite may be increased Bowel movements are usually normal Such cases usually show 4 000 000 to 5 000 000 red blood cells per cubic millimeter hemoglobin between 60 and 80 per cent, and slight or marked eosinophilia

Moderately severe cases show an exaggeration of the above symptoms The hair is dry and lusterless the expression of the face is dull there may be general itching of the skin the appetite may be voracious and the eating of earth or other mineral material may be indulged in although it is rarely admitted The tongue shares in the general pallor and may show atrophy of the papillae The bowels are usually constipated but there may be irregular intervals of diarrhea The heart shows slight hypertrophy the pulse is rapid and often weak and a hemic systolic murmur is usually heard over the precordium There is usually dyspnea on exertion There may be dizziness tinnitus and headache Weakness is marked fatigue is rapid and movements are slow There may be a slight amount of albumin in the urine with or without a few casts There may be edema of the feet The blood picture shows from 3 000 000 to 4 000 000 red blood cells per cubic millimeter The hemoglobin is between 30 and 60 per cent and eosinophilia is usually present

Severe cases show further intensification of the anemia and cardiac dilation Weakness and stupor are apparent Edema may involve the entire body including the face and the serous cavities and cardiac insufficiency may be present Slight exertion causes severe dyspnea The reflexes may be

abolished and paresthesias are present The skin is very dry The appetite may be enormous or poor The stomach may become dilated and nausea and vomiting are frequent Diarrhea may predominate over constipation The *stools do not contain gross* blood but occult blood is readily found The urine may show more albumin and casts These patients show between 2 000 000 and 3,000 000 red blood cells and 10 to 30 per cent of hemoglobin The color index sometimes exceeds 1 Eosinophilia is usually absent

In addition to the above symptoms hookworm disease retards general development Puberty is often delayed and if it occurred before infection took place sexual development may recede The age of the patient may appear five to ten years younger than it actually is Mental development is proportionately retarded In adults impotence may occur in men and menstruation cease in women

Diagnosis —The final diagnosis of hookworm infection is based entirely upon the demonstration of ova in the stools The simplest method is by a slide cover slip preparation of an emulsion of stool in water or saline A rough estimate of the intensity of infection may be gained from such a preparation but very light infections may be missed The salt flotation method in which an emulsion of about 1 cc of feces is made in 10 cc of a saturated solution of sodium chloride and allowed to stand for half an hour brings the eggs to the surface and permits the finding of very light infections Various methods have been developed for estimating the number of worms in the intestine and these are valuable in surveys of population groups in order to determine the clinical importance of the disease in such groups These methods however are not necessary in clinical practice since all persons harboring hookworms no matter how few in number should be treated for their removal The most important element in diagnosis is to keep the disease in mind in the presence of symptoms and to examine routinely the feces of every patient in areas where the disease might be present

Prognosis —Unless the patient is in the last stages of the clinical disease elimination of the worms should be followed by ultimate cure in the absence of reinfection Even the most severe cases may show dramatic improvement when the worms are eliminated and iron is administered Studies by Rhoads Castle and their associates have shown *however that in Puerto Rico* at least, chronic cases in which the anemia is pronounced do not improve rapidly after removal of the worms unless iron is given in large doses and that almost the same improvement in the blood picture can be obtained by the administration of iron without removal of the worms This emphasizes the importance of stimulating blood formation in hastening recovery from the disease

Treatment —A number of drugs have been advocated for the elimination of hookworms The chief problem has been to obtain a drug which is toxic for the worms but not toxic for the patient

Thymol finely particulated and mixed with an equal part of powdered lactose or sucrose in capsules and administered in a single dose of 4 Gm will remove about 50 per cent of the worms in one treatment The dose for children is 0 3 Gm per year of age up to twenty A few deaths following thymol have been reported but most of these were avoidable

Oil of chenopodium in three doses of 0.5 cc each in hard gelatin capsules at intervals of one half hour removes 70 to 90 per cent of the worms Children may be given 0 03 cc per year of age up to age fifteen A considerable number of deaths from this drug have been reported apparently due to idiosyncrasy or to excessive absorption

Hexylresorcinol in crystalline form in specially prepared hard gelatin capsules will remove 50 to 60 per cent of hookworms The adult dose is 1 Gm The dose for children is 0 1 Gm for each year of age up to age ten The advantage of this drug is that it is entirely nontoxic The crystals however will burn the mouth if the capsules are crushed and the drug combines quickly with organic matter so that food must be strictly avoided for twelve hours before and four hours after treatment

Tetrachlorethylene is probably the drug of choice because of its efficiency and lack of fatal toxicity No deaths have been reported Dizziness sometimes occurs The dose is 3 cc in hard gelatin capsules or in

skimmed milk given at one time Children may be given 0 2 cc for each year of age up to age fifteen This treatment will remove from 60 to 80 per cent of the worms If a heavy Ascaris infection is present with the hookworms Ascaris should be removed by hexylresorcinol before treatment for hook worms is given because tetrachlorethylene only stimulates Ascaris to activity and a large number of these worms might produce intestinal obstruction

Carbon tetrachloride should not be used as an anthelmintic because it may cause fatally toxic necrosis of the liver and is but little more effective than tetrachlorethylene

The toxic symptoms of thymol and oil of chenopodium usually appear from two to twenty four hours after treatment They are in general the same for the two drugs and consist of nausea vomiting dizziness stupor and coma They should be treated as early as possible by purging preferably with sodium sulfate and by general supportive measures

Preparation for anthelmintic treatment is important but can be overdone The patient should have a light evening meal without fats and should receive the drug in the morning before breakfast A preliminary purge is not necessary unless constipation is present Food should be omitted for a few hours and alcohol for twenty four hours after treatment A purge is usually advisable four hours after treatment in order to elim inate the worms and the drug Sodium sulfate is preferable to magnesium sulfate because the latter sometimes acts as a de pressant

Since one treatment with an anthelmintic rarely removes all of the worms the stools should be carefully examined for eggs five or six days after treatment and if they are found the treatment should be repeated at weekly intervals until the stools become negative

Iron should be given in large amounts The recommended daily dosage is 1 Gm of ferrous sulfate (exsiccated) in capsules or 6 Gm of ferric ammonium citrate in a 50 per cent solution These preparations should be given in three divided doses after meals It is best to start with smaller doses in order to avoid intolerance Children should receive doses in proportion to their weight This treatment produces rapid stimulation of reticulocytes and increase of hemoglobin and red blood cells with rapid general im provement of the patient. Liver extract is of no value except for its iron content The diet should be abundant and well balanced but this alone will not cause rapid improve ment unless it has a very high iron content

Prophylaxis —There are three important elements in prevention treatment the wear ing of shoes and sanitary disposal of ex creta Treatment is only of temporary value if reinfection can take place The wearing of shoes is dependent upon local customs and education The only effective method of prevention is sanitary disposal of excreta This must be adapted to the individual and community involved Since the larvae can not climb up a vertical surface to any height the deposition of excreta anywhere except on the ground is sufficient for prevention The bored hole latrine in many parts of the tropics and the pit privy in the rural por tions of the United States are sufficient to insure prevention if they are properly used Hookworm is still an important public health and clinical problem in many parts of the world including certain areas in the United States and will continue to be until sanitary disposal of excreta becomes uni versal

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HIRUDINEA

HIRUDINIASIS

(*Leech Infestation*)

HIRUDINIASIS is leech infestation Leeches are related to the earth worms They are segmented elongated oval objects usually concave on the ventral side and convex dorsally and possess two suckers one around the mouth and a blind one posteriorly They live primarily in water or in moist tropical environments Many leeches suck blood as a source of food They secrete *hirudin* an anticoagulin to prevent the blood from clotting after they have ingested it Their digestive tract is provided with numerous lateral diverticula capable of tremendous distention when the leech is engorging itself with blood

For centuries leeches have been used to let blood from patients While their previous utilization has been indiscriminate and usually ill advised there is probably justification for their application in certain types of essential hypertension and locally in certain cases of thrombosis and varicose veins For this purpose the cultivated medicinal leech *Hirudo medicinalis* is customarily employed

Injury Inflicted —Leeches are injurious to man in two ways externally and internally

External hirudiniasis is due to several species of land leeches which commonly live in tropical rain forests as in Ceylon Borneo the Dutch East Indies Australia Madagascar the lower valleys of the Himalayas and the northern Chilean Andes When man passes through such areas the leeches attach themselves to his skin even gaining entrance through heavy khaki pants and leather boots For the moment they cause practically no pain and are usually not noticed until the infested area of the body begins to ooze blood The wounds remain open for weeks become readily infected with pyogenic bacteria and heal with difficulty Occasionally profound exsanguination from multiple abandoned sites causes the death of the victim

REMOVAL OF LEECH —No attempt should be made to use force in pulling off a feeding leech lest the animal s jaws be left in the wound A few drops of brine or strong vinegar or a match flame applied to the worm will cause it to relax when it may be easily removed The wound should then be washed with a mild antiseptic solution, such as boracic acid staunched if necessary with a styptic pencil treated with calamine lotion and covered with an aseptic dressing

Internal hirudiniasis is most commonly caused by accidentally taking into the mouth in raw drinking water small leeches which become attached to the buccal mucosa epiglottis pharynx upper level of the esophagus naso pharynx larynx vocal cords trachea or even a bronchus The most notorious species of leech involved is *Limnatis nilotica* which lives in quiet brooks streams ponds and lakes in southern Europe northern Africa and the Near East while related species are found in west or central Africa and Malaya They may cause only moderate swelling of the area to which they become attached on the other hand they may produce painful or dangerous obstruction of passages with epistaxis hemoptysis or hematemesis at times leading to exsanguination, continuous coughing with slimy bloody discharge hoarseness or complete loss of speech pain in the nasal passage throat or chest dyspnea with or without cyanosis difficulty in swallowing and nausea suffocation at times leading to death Likewise persons wading or bathing in infected water may suffer infestation of the urethra urinary bladder or vagina

REMOVAL OF LEECH —If the leech is lodged in the upper respiratory passages it may be cocainized after it has been visualized then removed by gentle traction with an appropriate pair of forceps If the leech is in the posterior pharynx larynx trachea or bronchi the patient is placed in a Trendelenburg position the worm visualized through a bronchoscope cocainized and removed with greatest care The patient must be warned against taking a deep breath lest the leech be more deeply drawn into the respiratory tract Rarely tracheotomy is required to save the patient s life

On the other hand if the leech is lodged below the epiglottis in the upper level of the esophagus no fear may be experienced if it should be swallowed since it will be digested in the stomach For urogenital infestation strong saline irrigation is advised

PREVENTION —Care must be taken to filter or at least strain all water in infested areas before it is drunk

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ARTHROPODS AND HUMAN DISEASE

ARTHROPODS (Phylum ARTHROPODA) comprise the insects and their allies and constitute the largest assemblage of species in the Animal Kingdom Moreover many of the species exist in almost uncountable numbers While some of the arthropods are among man s best friends for the most part they are economically and medically harmful Members of this phylum are many celled invertebrates which are segmented along a longitudinal axis They possess a small body cavity and a large hemocelic cavity which penetrates into practically all the parts of the animal and is filled with the blood fluid They have a chitinous exoskeleton Most species have a tracheate respiratory system which penetrates to all the tissues of the body and obviates an intermediate lung for the exchange of oxygen and carbon dioxide As the phylum name implies arthropods have articulated appendages typically one pair for each body segment Each appendage is primitively made up of a basal portion and an inner and outer ramus but it is usually modified for purposes of walking swimming for sensory uses (i e antennae) for apprehending and crushing prey (i e chelae maxillae and mandibles) or for protection against enemies (i e venom apparatus at the anterior or posterior end of the body) The life cycle of an arthropod may be very simple or it may be very complex The main class groups of the arthropods of medical importance are as follows (I) The CRUSTACEA which have a fused cephalothorax and two pairs of antennae They comprise smaller forms (Entomostraca) including *Cyclops* and *Diaptomus* and larger forms (Malacostraca) including the crabs crayfishes and lobsters (II) The CHILOPODA or centipedes with several pairs of similar legs (III) The ARACHNIDA including the scorpions spiders ticks and mites with four pairs of walking appendages (IV) The INSECTA including lice bugs

beetles, bees wasps and ants moths and butterflies flies and fleas, all of which have three pairs of thoracic legs

Arthropods are medically important in three capacities (1) As causative agents of disease (2) as mechanical carriers of pathogenic micro organisms and (3) as necessary hosts (or incubators) and transmitters of pathogens to man In the first category are all of the blood sucking species those which venenate and those which actually parasitize the human body In the second group are those species especially flies which come in contact with disease producing organisms through their filthy feeding and breeding habits and then pass on the pathogens to man In the third group are the obligatory arthropod hosts of such agents of disease as the malaria parasites the filaria worms the rickettsias the relapsing fever spirochetes plague bacilli and others

Ernest Carroll Faust

ARTHROPODS AS CAUSATIVE AGENTS OF DISEASE

All blood sucking arthropods, *i e* ticks many species of mites lice blood sucking bugs, blood sucking flies and fleas puncture the skin and introduce minute amounts of saliva into the puncture wound before taking a blood meal If the puncture wound is small as in the case of mosquitoes and other blood sucking gnats the trauma is slight but the protein in the introduced saliva may lead to allergic reactions with local or generalized edema and inflammation accompanied by fever In the case of ticks the wound is moderately large and may become ragged if attempts are made to remove the tick with its mouthparts unrelaxed Moreover red mites (chiggers) usually bury their heads in the skin of their victim so that removal is difficult The sarcoptic mite (*Sarcoptes scabiei*) actually tunnels in the skin and multiplies there and the follicular mite (*Demodex folliculorum*) utilizes the hair follicles for similar purposes The female chigoe (*Tunga penetrans*) burrows into the skin to secure food for the development of her eggs

The **sarcoptic or itch mite** is widely prevalent in charity clinics and in groups of the population with low personal hygiene The disease is known as *sarcoptic mange* The female which measures 330–450 microns in length by 150–200 microns in breadth has a slightly projecting head (*capitulum*) and four pairs of short conical legs She burrows into the skin *via* hair follicles and develops a somewhat tortuous tunnel several millimeters to a few centimeters in length and nearly parallel to the skin surface At the inner end of the tunnel she lays about forty ovoidal eggs over a period of four to five weeks Within three to five days after oviposition a six legged larva hatches from each egg The larvae develop lateral burrows or come out of the tunnel and produce new burrows Four to ten days later they have moulted and have become sexually mature New sites of infestation develop in this way in the skin of the same individual, or from his clothing or bed linen infest his associates

The *lesions* develop rapidly as raised red linear channels in the epidermis and are most common between the fingers on the backs of the hands elbows axillae groin breasts umbilicus penis shoulder blades and the small of the back Deposition of little fecal pellets by the mites in their burrows produces vesiculation with itching which is intensified by warmth and moisture Scratching produces an open weeping lesion which frequently becomes infected with pyogenic bacteria

Diagnosis is based technically on the recovery of the mites from the inner ends of the tunnels but the lesions are so characteristic that clinical diagnosis is relatively satisfactory

Prognosis is good with persistent treatment

Treatment—Sulfur ointment (5 per cent flowers of sulfur in lanolin) is commonly used but the more complicated Danish treatment is preferred by some physicians After all suspected lesions have been scrubbed with green soap and soaked in warm water the ointment is rubbed in before the patient retires The next day fresh clothing is put on and all soiled clothing and bed linen are sterilized by boiling This is repeated the second night and at least once again between the sixth and tenth nights to kill larvae freshly hatched from eggs For individuals sensitive to sulfur pyrethrum

ointment (0 75 per cent pyrethrins one part lanolin 2 parts and vaseline one part) or 2 per cent rotenone in vaseline may be substituted

Graham (1943) recommends a single painting of the entire skin from neck to soles of scabies infested patients following a hot bath with a 20 per cent emulsion of benzyl benzoate the effective principle in balsam of Peru He claims about 99 per cent cures disregards the possibility of reinfestation from fomites and states that the procedure is highly practical for military and civilian cases

Pediculosis is louse infestation and may refer to head lice (pediculosis capitis), body lice (pediculosis corporis) or pubic lice (pediculosis pubis) Head lice (*Pediculus humanus var capitis*) infest the head and attach their eggs near the base of the hair shafts body lice (*P humanus var corporis*) feed on the skin but usually attach their eggs to the fibers of body clothing pubic lice (*Phthirus pubis*) live closely appressed to the skin usually in areas of the pubic axillary and breast hairs occasionally in the eyebrows and eyelashes attaching their eggs to these hairs They all produce an irritating roseate papular dermatitis

Treatment —For *head lice* the hair should be cut short and the head skin thoroughly rubbed with crude petroleum and olive oil half and half then after several hours cleaned out with soap and water and the eggs combed out with a fine toothed comb For *body lice* any organisms feeding on the skin should be removed with forceps the body hairs should be shaved off and the lesions treated with 1 per cent thymol in alcohol to relieve the pruritus All clothing and bed linen mattresses etc should be sterilized by dry or steam heat fumes of methyl bromide in a closed container or dry cleaning processes For *pubic lice* crude petroleum and olive oil half and half or 10 per cent thymol in olive oil should be thoroughly rubbed into the infested areas except that in infestation of the eyelashes these antiseptics are too strong and individual lice and eggs must be removed with forceps

Bites.—For *treatment of dermatitis* due to bites of flies fleas mites and others application locally of phenolated camphor in pure mineral oil ('Campho phenique) is a satisfactory well tolerated palliative which will usually prevent sepsis

Myiasis —The largest group of tissue invaders among the arthropods is that of fly larvae (*i e* maggots) producing myiasis The mother fly may lay eggs on food or in drink which is accidentally taken into the digestive tract and produces temporary *intestinal myiasis* or may by design deposit eggs or young maggots in or nearby a wound or on the unbroken skin The maggots hatching from eggs or those already hatched invade the whole or damaged skin or mucous membranes and cause *cutaneous ophthalmic rhinal aural* or *urethral myiasis* Many of these infestations are nonspecific or only semi specific as in the case of house flies green bottles blue bottles stable flies and some species of flesh flies On the other hand specific infestation is intentional as in the case of the primary screwworm fly (*Cochliomyia hominivorax*) the sheep bots (*Oestrus ovis*) the cattle bots (*Hypoderma bovis* and *H lineatum*) the horse bots (*Gasterophilus* spp) and the tropical warble fly (*Dermatobia hominis*) Some of the semi specific and all of the specific myiasis producing flies frequently cause permanent disfigurement of the invaded skin and underlying tissues and may be responsible for death of the victim especially in case of small children Moreover wounds infected secondarily with pyogenic bacteria are much more difficult to handle than uncomplicated ones *Surgical removal* of these maggots should be accomplished as soon as diagnosis has been made

The **venenating arthropods** include centipedes scorpions spiders some ticks bees, wasps and ants blister beetles and the caterpillars of several moths

Centipedes have a pair of hollow oral fangs which are provided with basal poison glands through which venom is introduced into the victim when the fangs penetrate the skin This produces local and at times general inflammation but probably never has a fatal termination

True scorpions have a single curved hollow caudal fang through which the venom elaborated in a pair of basal glands is emptied into the skin This venom contains neurotoxins hemolysins and endothelio-

lysins In many warm countries, including the southwestern United States species of *scorpions frequently* venenate human beings whose skin accidentally contacts the scorpion as the unprotected surface of the foot or arm In Durango State, Mexico, in Trinidad, and in parts of India and Africa death especially in small children is not uncommon as a result of scorpion sting with ascending motor paralysis at times accompanied by acute pancreatitis Specific antivenins can be prepared but are not generally available Insulin has been recommend to combat the pancreatitis Caution should be exercised to prevent direct skin contact with these creatures

Spiders—All spiders are venomous but only a few species are able to penetrate human skin with their pair of oral fangs" through which the venom is discharged The most notorious spider is the 'black widow" (*Latrodectus mactans*), which has a wide distribution from Canada to Chile Its venom is a toxalbumin containing fractions which produce both an ascending motor paralysis and destruction of peripheral nerve endings There is sharp pain swelling and reddening at the site of the 'bite' dizziness and weakness, tremor of the legs and abdominal cramps after lymphatic absorption of the venom Board like rigidity and spasm of the abdominal muscles may simulate an acute appendix or tetanus More advanced symptoms include urinary retention reduced heart beat and feeble pulse labored breathing and speech light stupor convulsions in small children and delirium

TREATMENT—With a history of black widow spider 'bite" (*arachnidism*) the patient should be placed in bed given 10 cc of a 10 per cent solution of calcium gluconate intravenonusly to reduce pain and to protect peripheral nerve endings and then given immune serum (Antivenin *Latrodectus Mactans* Mulford s) Care must be exercised not to disturb black widow or other dangerous spiders lurking in their webs in caves, under rocks around the base of posts or lumber piles or on the under side of the seats of outdoor privies

Ticks—The Rocky Mountain wood tick (*Dermacentor andersoni*) and some other species of hard bodied ticks introduce a poison into the skin along with their saliva, causing an ascending motor paralysis This has been experimentally demonstrated not to be a neurotoxic virus It is most concentrated in adult females which have not previously fed and most dangerous when the tick bites at the base of the medulla No specific relief has been developed Abbott has recently provided a comprehensive review of the epidemiology and clinical aspects of tick paralysis

Bees and *wasps* have a posterior sting apparatus the modified ovipositor through which venom is introduced into human skin The venom consists of acid and alkaline fractions and a histamine like fraction Honey bees deposit the entire sting apparatus in the wound For most persons the wound is painful and may produce mild systemic reaction Some sensitized individuals die as a result of repeated stinging unless treated with epinephrine They should then be desensitized with whole bee venom made up in Coca s solution *Blister beetles* contain a vesicant which produces blisters when the coxal or body fluid of the beetle is discharged on the skin Mild applications as damp baking soda should be applied topically Many types of *moth larvae* (*i e* caterpillars) possess hollow poison hairs, at times concealed by tufts of nonpoisonous hairs In contact with human skin the poison hairs discharge minute amounts of an urticating substance which behaves like a chemical burn and heals with difficulty Palliative treatment consists in the application of calamine lotion

ERNEST CARROLL FAUST

ARTHROPODS AS MECHANICAL CARRIERS OR ESSENTIAL HOSTS

As Mechanical Carriers of Pathogenic Micro organisms—Due to their filthy feeding and breeding habits many of the common flies are able to serve as mechanical vectors of several pathogenic organisms affecting man These flies (common house fly lesser house fly biting and non biting stable flies green bottles blue bottles, blow flies flesh flies fruit flies etc) commonly feed on garbage and the dung of man and domestic animals Usually they oviposit or larviposit on such decaying organic material

and the larvae (i e maggots) feed and grow in these media After a pupal stage during which the apparently resting organism undergoes a profound internal reorganization, the adult fly emerges from the pupal case privy or other deposit of human feces and the fly next alights on human food or utensils in the kitchen or on the dining table not only are pathogenic micro-organisms likely to be transferred in vomit drops or

TABLE 1 —THE ROLE OF ARTHROPODS IN THE TRANSMISSION OF IMPORTANT DISEASES TO MAN

DISEASE	ETIOLOGIC AGENT	ARTHROPOD TRANSMITTERS	ETIOLOGIC AGENT IN THE ARTHROPOD S BODY
Yellow Fever	Unnamed filtrable virus	Mosquitoes especially *Aedes aegypti*	Multiplication (proboscis inoculation)
Dengue	Unnamed filtrable virus	*Aedes aegypti* *A albopictus*	Multiplication (proboscis inoculation)
Equine Encephalomyelitis	Unnamed filtrable virus	Mosquitoes (*Aedes* spp)	Multiplication (proboscis inoculation)
Pappataci Fever	Unnamed filtrable virus	Sand flies (*Phlebotomus papatasii*)	Multiplication (proboscis inoculation)
Oroya Fever	*Bartonella bacilliformis*	Sand flies (*P peruensis* *P noguchii*)	Multiplication (proboscis inoculation (?))
Typhus Fever Epidemic (Classical)	*Rickettsia prowazeki*	Louse (*Pediculus humanus*)	Multiplication in epithelial cells of gut wall (inoculation from bite feces or crushing on skin)
Endemic (Murine)	*Rickettsia prowazeki*	Rat flea (*Xenopsylla cheopis*)	Multiplication in epithelial cells of gut wall (inoculation from bite)
Tick Typhus (Rocky Mt and related fevers)	*Rickettsia rickettsi*	Hard bodied ticks (*Dermacentor andersoni et al*)	Multiplication in epithelial cells of gut wall (hypostome inoculation)
Japanese River Fever	*Rickettsia orientalis*	Red mites (*Trombicula* spp)	Multiplication in body (hypostome inoculation)
Relapsing Fever Epidemic	*Borrelia recurrentis*	Louse (*Pediculus humanus*)	Multiplication in tissues outside gut wall (inoculation from crushing lice on skin or from bite of tick)
Endemic	*Borrelia duttoni*	Soft bodied ticks (*Ornithodoros* spp)	
Plague	*Pasteurella pestis*	Rodent fleas especially *Xenopsylla cheopis*	Multiplication in gut (proboscis infection)
Malaria	*Plasmodium vivax* *P malariae* *P falciparum* *P ovale*	Mosquitoes (many species of *Anopheles*)	Sporogony (saliva infective proboscis inoculation)
Kala azar	*Leishmania donovani*	Sand flies (*Phlebotomus* spp)	Metacyclic development (saliva infective proboscis inoculation)
Cutaneous leishmaniasis	*Leishmania tropica*	Sand flies (*Phlebotomus* spp)	Metacyclic development (saliva infective proboscis inoculation)
Muco-cutaneous leishmaniasis	*Leishmania braziliensis*	Sand flies (*Phlebotomus* spp)	Metacyclic development (saliva infective proboscis inoculation)
African trypanosomiasis	*Trypanosoma gambiense*	Tsetse flies (*Glossina palpalis*)	Metacyclic development (saliva infective proboscis inoculation)
	Trypanosoma rhodesiense	Tsetse flies (*Glossina morsitans*)	
Chagas Disease	*Trypanosoma cruzi*	Cone-nosed bug	Metacyclic development (feces infective when rubbed into skin)
Filariasis Bancrofti s	*Wuchereria bancrofti*	Mosquitoes (especially *Culex fatigans*)	Larval development without multiplication escape from tip of proboscis sheath onto human skin
Onchocercosis	*Onchocerca volvulus*	*Simulium* spp	
Loaiasis	*Loa loa*	*Chrysops* spp	

dries its wings and flies about to take food It feeds on dissolved and finely particulate material which it sucks up into its proboscis After ravenously feeding it defecates and vomits If the feeding ground is an open fecal pellets to food drink or containers but moist feces temporarily lodged on the outside of the fly s body (i e proboscis trunk and legs) may be a source of contamination

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Role in Epidemics—Substantial proof has been furnished that filth flies have been responsible for epidemics of several enteric diseases including typhoid fever, bacillary dysentery, cholera, and amebic enteritis Moreover, suspicion has recently been again directed to filth flies in the transmission of infantile paralysis and it is epidemiologically possible that trachoma may be mechanically contracted from flies which breed in profusion in regions like India and Egypt Biting stable flies contaminated with horse manure, may introduce tetanus and anthrax spores into the skin Eye gnats (*Hippelates* spp) have been incriminated in epidemics of acute conjunctivitis ('pink eye') and are potential vectors of the spirochete of yaws

Control of epidemics of several of the above mentioned diseases at times depends primarily on *control* of *fly breeding* Homes should be adequately screened garbage cans should be tightly covered, the garbage collected daily and completely incinerated, outdoor privies should be soundly constructed should be screened and the pit kept clean with generous frequent applications of quick lime or crude oil Barnyard manure should be adequately treated and drained to prevent the breeding of stable flies In cities where screening and sanitary disposal of garbage are carried out the dangers of fly convection of pathogenic micro organisms have been greatly reduced But in rural areas particularly on large farms flies are still a menace to human health

While flies constitute the greatest danger with respect to the mechanical transmission of disease bedbugs mosquitoes and other blood sucking arthropods have been found experimentally to be suitable mechanical carriers of *Pasteurella tularensis* and the virus of yellow fever

As Essential Hosts (or Incubators) of Pathogenic Micro organisms—The disease entities for which arthropods play an essential role in development or multiplication and transmission to man are considered in other chapters of this book Hence it is desirable to call attention here only to the relation of arthropods to these etiologic agents This can be most concisely presented in tabular form (Table 1)

In conclusion it may be stated that arthropods constitute a most important part in the causation of human diseases including many endemic infections, but particularly certain epidemic diseases for which certain arthropods are the necessary transmitters Intelligent recognition of these facts by the physician will assist materially in the control of many of these diseases

ERNEST CARROLL FAUST

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DISEASES OF DOUBTFUL OR UNKNOWN ORIGIN

RHEUMATIC FEVER

(Acute Rheumatic Fever Acute Articular Rheumatism Acute Rheumatism Polyarthritis Rheumatica)

Definition —Rheumatic fever is a disease infectious in nature closely associated with invasion of the body by Group A hemolytic streptococci; it is characterized by febrile and toxic states by the presence in various parts of the cardiovascular system and joints of multiple disseminated focal inflammatory lesions and at times by serofibrinous inflammation of some of the great mesothelial lined body cavities and joints it is further characterized by a tendency for the febrile toxic and arthritic signs to disappear following the exhibition of certain antipyretic drugs in sufficient doses

Incidence.—Neither rheumatic fever nor rheumatic heart disease are reportable hence the incidence must be estimated indirectly Heart disease is among the first three causes of death in the first four decades of life in New York State There are probably between 30 000 and 60 000 deaths from rheumatic heart disease per year in the United States and at an estimated rate of 1500 to 2000 new cases per million population there would be between 200 000 and 260 000 cases of rheumatic fever per year There is considerable evidence of a falling incidence and death rate from decade to decade

Morbid Anatomy —The typical pathologic unit is a submiliary granuloma variation in location size and stage of development of these granulomata account for most of the pathologic pictures According to Klinge the earliest evidence of injury is a fibrinoid swelling of the ground substance of the connective tissue This swollen ground substance stains like fibrin Usually the collagen fibers remain intact but not infrequently small areas of fragmented fibrils are seen In this early period wandering granulocytes are encountered In from ten to fourteen days these areas are surrounded by the characteristic rheumatic granuloma cells These have basophilic cytoplasm, large vesicular nuclei frequently multiple often containing masses of dense staining chromatin McEwen showed that they probably arise from undifferentiated mesenchymal elements of connective tissue Granulocytes may persist and a few lymphocytes and plasma cells appear usually the granuloma cells gradually elongate and assume the appearance of fibroblasts until finally a scar is formed

The myocardial Aschoff body is the most typical rheumatic granuloma comparable lesions elsewhere are modified by the structure of the tissue involved Thus subcutaneous nodules are probably conglomerations of submiliary granulomata occurring in structures capable of responding more vigorously to local tissue injury than is the myocardium Similar submiliary foci are seen in the periarticular tissues and synovial membranes but there is in addition a marked increase in viscid synovial fluid containing fibrin clasmatocytes and wandering cells and the periarticular tissues are diffusely edematous Under the influence of certain antipyretic drugs the exudative components quickly disappear but the proliferative phenomena are more persistent

In rheumatic pericarditis and pleurisy the exudate is serofibrinous in the former the fibrinous characteristics may be very marked and the normal endothelial covering may be entirely destroyed and eventually replaced by organization of the exudate into fibrous tissue with partial or complete obliteration of the pericardial cavity In pleurisy less fibrin is encountered and adhesions even though present are less extensive

Rheumatic valvulitis ordinarily called endocarditis is more clearly understood if considered from the viewpoint already advanced In the gross there is a deposit of small grayish pink verrucae along the surfaces of the valves at the lines of contact of opposing cusps together with thickening of the valves Microscopically the vegetations

consist of fibrin enmeshing various cellular blood elements deposited on a portion of the valve from which the endothelium has been denuded In the substance of recently involved valves as yet practically free of verrucae there are at times areas closely resembling Aschoff bodies Small foci of proliferative inflammation with rapid vascularization are usually seen Probably the primary process is in the region of the valve rings from which an interstitial inflammation extends into the cusps, and the throm

hearts These lesions were often demonstrable only by careful microscopic examination Healing is effected by vascularization of the verrucae and by scar formation in both the valve and vegetation the endothelium at the bases of the verrucae grows over the surface and a thickened scarred less flexible valve is the usual result This valve moreover is a *locus minoris resistentiae* possibly due to its vascularity, or to the fact that the mobile scars being composed chiefly of collagen, are tissues particularly

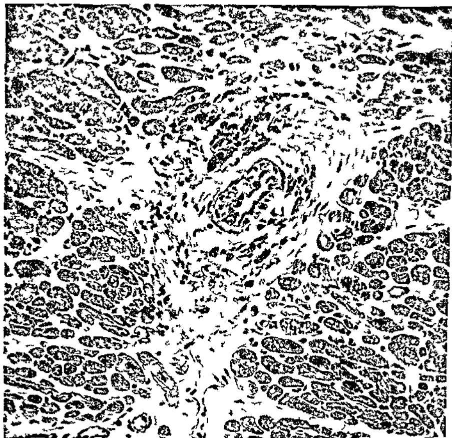


Fig 59—Perivascular granulomata (Aschoff bodies) in heart of patient with chronic myocarditis and valvulitis Note also endovascular lesions Eosin and methylene blue stain

botic verrucae appear to be secondary in nature, their localization is apparently due to mechanical trauma which causes the valvular endothelium already swollen and proliferated as a result of the underlying inflammation to be destroyed at the points of most violent impact with opposing cusps Indeed Holsti has shown that interstitial valvulitis is present in the majority of valves of the left side of the hearts of patients dying from rheumatic carditis and in about one half of the valves of the right side of the

liable to attack by the 'rheumatic poison Thus the valves of a patient who has suffered from 2 or more attacks of rheumatic fever show evidence of the previous attacks in scar formation and increased vascularity and of the last attack in new focal proliferative lesions and recent vegetations

Rheumatic granulomata not infrequently occur under and in the mural endocardium especially in the left auricle as first observed by MacCallum Pappenheimer and von Glahn and many others have described

them in the aortic adventitia with small focal scars in the media and collections of granuloma cells about the vasa vasorum In many visceral blood vessels inflammatory lesions have been seen The endothelium is swollen and separated from the wall by fibrin which may invade the entire vessel wall and be mixed with cellular debris and fragmented elastica Surrounding the vessel there may be hemorrhage exudate and typical cells very comparable to that seen in auricular endocarditis Holsti states that arteritis verrucosa is most frequently encountered in the peritonsillar and intestinal blood vessels of rheumatic subjects This lesion consists of fingerlike projections from the vessel wall into the lumen these projections are covered with elastica continuous with that from the arteries Gray and Aitken describe eccentric fibrous thickenings of small veins It thus is obvious that the poison active in this disease may affect most portions of the cardiovascular tree

In chorea minor which is probably a rheumatic affection of the brain there are disseminated focal endo and perivascular lesions and at times zones of focal encephalitis also some neuroglial increase While apparently having little similarity to cardiac granulomata it must be recalled that outside the blood vessels the brain has relatively little mesenchymal tissue hence can not respond histopathologically like other parts of the body

Etiology — *Predisposing* — Rheumatic fever is especially prevalent in the temperate zones less in the subtropics is rarely seen in the West Indies but lately has been frequently reported in the East Indies In elevated tropic areas having colder climates more cases may be encountered and there is a parallel incidence of scarlatina erysipelas and puerperal fever Several clinicians have noted that the polyarthritic manifestations are relatively milder in the southern part of the United States compared with carditis and although classic inflammatory rheumatism is said to be rare in the Central and Great Plain States mitral stenosis is common Such data point to climatic influence on both incidence and clinical manifestations

Most cases occur in the late winter and early spring the season of most frequent respiratory infection

Damp areas such as water fronts and concealed water courses seem to favor development of the disease possibly because in these zones occurs more poverty with its attending malnutrition crowding and unhygienic environment conducive to the spread of respiratory infections Rheumatic fever is more prevalent among the poor than in the well to do Coburn found a ratio of 20 1 in New York City and Gunewardene observed

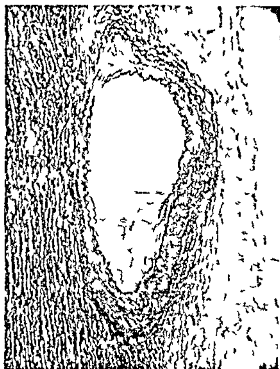


Fig 40 —Rheumatic lesion of coronary artery in a patient with accidental death nineteen days after onset of first attack of rheumatic fever Splitting of elastica and early embolus Weigert s elastica stain

a relatively high incidence among the poor in Ceylon

Multiple cases in a family are fairly common This may be due to at least two factors (1) an inherited tendency or weakness (2) common exposure to an infectious agent Not infrequently several members of a family show symptoms of upper respiratory streptococcal infection but only one develops rheumatic fever

The disease rare in infants begins to appear in children about five years of age increases in frequency until the age of nine to eleven after which the curve of relative in

cidence falls While most cases occur within the first three decades the infection is often active in later life, for example, Pappenheimer and von Glahn found 45 per cent of their active fatal rheumatic carditis in subjects more than thirty years old Polyarthritis is relatively more frequent among men Females, on the other hand suffer more from mitral stenosis in adults and from chorea among girls

Epidemics have been described in isolated communities boarding schools military camps hospital wards and convalescent homes These accompanied or followed epidemics of tonsillitis nasopharyngitis or scarlet fever which recent studies have shown to be due to Group A hemolytic streptococci This indicates that the contagious element resides in the precursory streptococcal disease

Bacteriology—There is very little conclusive evidence that non hemolytic streptococci occasionally recovered in blood cultures or at autopsy play a role in the causation of rheumatic fever Neither has any filtrable virus or pleuropneumonia like micro organism been shown to be etiologically important The agglutination of minute particles isolated from rheumatic exudates and once thought to be viral in origin (Schlesinger and co workers) was subsequently proven to be nonspecific (Eagles and Bradley) the particles are probably degeneration products of inflammatory cells or tissue

The most constantly demonstrable micro organisms associated with attacks of rheumatic fever are hemolytic streptococci belonging to Group A (Lancefield) These streptococci are demonstrable in the throats of between 50 and 75 per cent of patients at the time of onset of an attack of rheumatic fever On the other hand when it has been possible to make repeated cultures during the month prior to the onset Group A hemolytic streptococci have been demonstrated in almost all the patients Not infrequently they are present in nose cultures and absent in those from the throat and nasopharyngitis may be so mild as to escape detection without bacteriologic examination Obviously only a fraction of patients with streptococcal nasopharyngitis develop rheumatic fever, the proportion is much higher in those who have suffered previous rheumatic attacks Streptococci belonging to groups other than A do not induce attacks of rheumatic fever, neither does non streptococcal nasopharyngitis The prevention of both streptococcal respiratory infections and rheumatic fever by prophylactic doses of the sulfonamides is additional proof of the etiologic role of streptococci in respect to rheumatic fever

Most rheumatic fever patients develop relatively high titers of both antistreptolysin O and antifibrinolysins in their blood serum these are manifestations of the precursory hemolytic streptococcal infections Some observers (Coburn and others) claim that the antistreptolysin O titers are higher and more prolonged in rheumatic subjects than in nonrheumatics While this may be true when patients with simple streptococcal tonsillitis or nasopharyngitis are employed as controls those with more deep seated or persisting streptococcal infections have equally marked titers Todd Coburn and Hill have reported that rheumatic fever patients have a lower content of so called anti streptolysin S in their serum than do non rheumatic controls and that this anti streptolysin increases with recovery We have found that patients with prolonged low grade rheumatic fever were slower in developing type specific anti M precipitins than were streptococcus infected nonrheumatic subjects or rheumatic subjects who recovered rapidly The theory may thus be advanced that recovery from rheumatic fever is associated with the development of efficient type specific antistreptococcal immunity

How the hemolytic streptococcus induces rheumatic fever is not known The symptoms appear not with the initial bacterial infection but after an interval of one to four or five weeks usually in the third week This is the period when bacterial allergy *i e* hyperergy appears after an infection Similar hyperergy may be induced in animals by focal injections and it is heightened by repeated foci of streptococci Hypoergy is induced by intravenous injections of similar micro organisms and by the development of type specific immunity The type specific immune capacity of an antistreptococcal serum runs parallel to its anti M precipitin

content Theoretically, then the development of a suitable degree of type specific immunity should result in the elimination of a streptococcal infection, while on the other hand chronic focal infection and only a low grade immunity might result in a hypergic state which would account in part for some of the rheumatic symptoms Such an hypothesis is at least reasonable

essential lesion) is a soluble poison of some sort as yet unrecognized

Symptoms —While this disease is usually considered as one having pyrexia toxemia and migratory polyarthritis as its main features this description is one of convenience only and other essential features must be kept in mind if its nature is to be clearly comprehended The symptoms of rheumatic

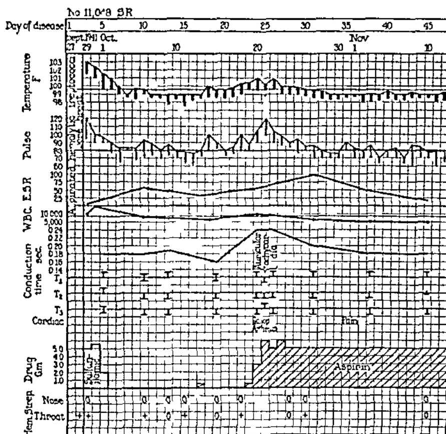


Fig 41 —Chart of a case of rheumatic fever induced by an accidental laboratory pharyngeal infection with hemolytic streptococci Although this streptococcal infection was controlled by sulfanilamide there were definite signs of rheumatic fever twenty days later These responded to aspirin During the so-called latent period (phase 2) the electrocardiogram showed diphasic T wave in lead 1 and negative T waves in leads 2 and 3 indicating cardiac involvement with the onset of rheumatic fever the PR interval increased to 0.24 of a second and there was auricular tachycardia The electrocardiogram returned to normal about the 75th day

The irritant might be particulate (bacterial bodies) or a soluble substance either from the streptococci their metabolic products or from the infected tissues Green and Collis claim that hemolytic streptococci may be cultured from the rheumatic heart valves but this has not been substantiated in our laboratory when strict surgical technique was used at the autopsy It seems more probable that the agent responsible for inducing the focal injury of the collagen (the

fever moreover as seen today are usually markedly altered by antipyretic drugs which while affording comfort also carry with them the danger of blinding both the physician and the patient to manifestations of infection in some important organ

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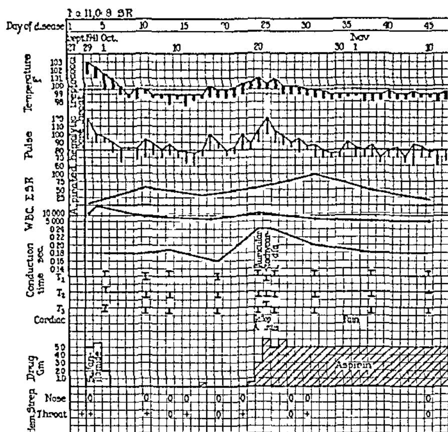


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coccal infection there is usually a latent period when the patient may feel perfectly well or have symptoms so slight that their significance is not evident until the onset of the rheumatism Careful study, both clinical and laboratory, of the patients in this latent phase not infrequently yields evidence of cardiac involvement

The onset of rheumatic symptoms may be gradual or acute apparently precipitated by chilling or overexertion Within a day the acute disease is often well developed, with a fever of 102° to 104° F, rapid pulse profuse perspiration, severe prostration, and polyarthritis It is rare for the inflammation to begin simultaneously in all of the joints, those most subject to stress and strain are first affected Initially monarticular arthritis is rare, it is more common to have the symmetrical joints simultaneously affected The striking feature of the arthritis is its migratory character, new joints are involved in rapid succession Various modes of extension described by different observers need not be here detailed While any joint in the body may be inflamed the large joints are most often implicated some claim that early involvement of the fingers and toes prognosticates a more chronic type of disease

A single involved joint usually manifests all the signs of acute inflammation *viz* pain tenderness swelling heat and local redness The swelling is due both to an effusion into the joint cavity and to edema of the periarticular structures Pressure from the exudate probably accounts to a considerable degree for the pain because there is often marked local relief following the aspiration of fluid from a joint Because of tenosynovitis the local manifestations must be considered not only as an arthritis but as an inflammation of any structure in proximity to a synovial membrane While the turbid fluid aspirated from these joints shows a marked increase in cells at times 20 000 to 30 000 per cubic millimeter suppuration does not occur unless there is secondary infection by pyogenic bacteria Disappearance of arthritis especially in children and young adults is accompanied by complete restoration of function without gross alteration in structure in older people on the other hand slight morning pain and stiffness often persist for several weeks

The polyarthritic form of the disease may be conveniently divided into monocyclic polycyclic and continuous In the first there is a single cycle of fever lasting from ten to fourteen days, the arthritis spreads from one set of joints to another with an increase in pyrexia as each new set is involved each joint is inflamed from four to six days then recovers and is not again affected after involvement of few or many of the joints the fever decreases the arthritis diminishes and the patient recovers without further manifestations In the polycyclic form on the other hand following a single cycle such as described there may be recurrence of another cycle of the same type or joints that have recovered may again become inflamed before completion of the first cycle and thus the two be superimposed The administration of salicyl shortens these cycles, but persistence of infection may be shown by the recurrence of arthritis and fever as the influence of the drug wears off In the continuous form the patient always presents some indication of active infection often varying in intensity from time to time In both the polycyclic and continuous forms the physician should be especially alert to detect serious involvement of the heart

Cardiac involvement is one of the most common features of rheumatic fever and is detected in proportion as our methods of examination are refined and applied Thus daily or semiweekly electrocardiograms showed transitory abnormalities in more than 95 per cent of our patients These variations occurring at any time may be the chief signs of a re awakening infection While such graphic records are impossible in all cases repeated careful physical examinations will frequently reveal evidence of cardiac involvement Obvious signs of cardiac embarrassment are easily detected and need not be here discussed but less marked signs require consideration Precordial pain and hyperesthesia point to myocardial involvement usually quite unaccompanied by pericarditis Gross changes in the size of the heart detectable by percussion are indicative of marked dilatation or of pericardial effusion Early significant roentgenographic alterations in the size of the heart are less frequent than would be expected

A diffuse precordial impulse wavelike in character indicates that the heart muscle is not contracting normally One can at times feel at the apex or just above and mesial to it, an extra impact synchronous with an intensified third heart sound This gives the palpatory evidence of a gallop more easily heard when felt however, it is a sign of unusual cardiac action

While it is impossible to be dogmatic concerning the interpretation of abnormal auscultatory signs much valuable information can be gained by listening to the heart daily Cardiac rate will be discussed later A change in auscultation rhythm is fairly common most frequently it is expressed as a gallop apparently due to an accentuation of the third heart sound which is at times as intense as the second sound Gallops usually come and go hand in hand with other evidence of cardiac involvement While most common in children and adolescents at an age when a third heart sound is most readily detectable they are often present in adults The tick tack rhythm of embryocardia is usually accompanied by obvious cardiac dilatation and other evidence of heart failure and is always a serious omen Aside from the usual sinus arrhythmia of children irregularities in rhythm are due to premature contractions to heart block usually partial or to auricular fibrillation Sometimes extrasystoles are frequent and regular enough to give coupled beats again they occur in uneven groups suggesting auricular fibrillation at other times they appear only once or twice a minute The regular dropping of a ventricular systole every four to seven beats points to partial heart block this suspicion can be confirmed by electrocardiograms Partial blocks usually persist only a few days Rarely complete heart block with bradycardia is encountered

Complete irregularity due to auricular fibrillation occasionally occurs and indicates a severe degree of cardiac involvement it usually is not persistent Some patients after recovering have resumed their normal laborious occupations without a return of cardiac irregularity

Murmurs detected during the course of an attack of rheumatic fever are difficult of interpretation especially when systolic in time Such systolic murmurs audible over the lower left precordium are frequent and usually explained as due to dilatation of the valve rings resulting in a slight relative insufficiency If we predicate that there is first an interstitial valvulitis with edema and subsequent deposition of verrucae we must conclude that some of the regurgitation at least is due to imperfect approximations of the leaflets Many patients have a very soft blowing diastolic murmur along the left sternal margin from the third to the fourth interspaces at times audible at the apex best heard by direct auscultation and unaccompanied by low diastolic pressure Occasionally such murmurs recur with other evidences of renewed infection Sometimes after recovery they disappear permanently again obvious signs of aortic insufficiency eventually develop The final significance of these murmurs must often be determined by studying the patient for months or years

While early interstitial inflammation doubtless at times prepares the valves for subsequent deformation more often crippling degrees of scarring depend upon long persistent or recurring involvement of the valves Not infrequently loud murmurs persist without cardiac embarrassment in patients who have fully overcome their infection, again only slight physical signs of valvular defects are found in others who are the subjects of marked cardiac insufficiency The degree of myocardial involvement therefore is as significant as the thickening of the valve or the dilatation of its ring

Pericarditis in rheumatic fever practically always is accompanied by an underlying myocarditis hence the importance of its detection Precordial pain occurring in a rheumatic fever patient is probably due more to a myocardium laboring under great handicap than to inflammation of the covering membranes One who awaits the appearance of precordial pain before suspecting pericarditis will fail to detect many instances for pericarditis often is unaccompanied by pain More significant is a to and fro friction rub which if of a double shuffle character is pathognomonic Such rubs may persist for days or occasionally last only a few hours With the accumulation of large amounts of fluid in the pericardial sac the rubs decrease or disappear they often persist however in spite of the outpouring of exudate The high

fibrin content of these exudates may explain in part the persistence of a rub and the insignificant reduction in the areas of precordial dulness and flatness after paracentesis Accumulation of exudate is indicated by increase in the area of precordial flatness and by a triangular area of marked dulness or flatness posteriorly in the region of the angle of the left scapula with distant bronchovesicular breath sounds and egophony over this area There occur also general symptoms and signs of weakened heart action dependent both upon pressure from accumulated fluid and upon concomitant myocarditis The patient should be followed upon recovery for signs of adhesions between the two layers of the pericardium for such adhesions are often the cause of severe permanent cardiac insufficiency

The *pulse* generally reflects the condition of the heart, hence alterations in cardiac rhythm and rate are immediately indicated in pulse records As alterations in rhythm have already been mentioned only rates or special features need be discussed here Early in polyarthritic forms of the disease acceleration in rate is proportional to the fever later it is indicative of myocardial damage Often a relapse in which the heart is the principal site of infection is indicated by rapid pulse If a high pulse rate persists in spite of normal temperature or low grade fever myocarditis should be suspected Marked and persistent increases in rate following slight exertion are very suggestive of injury to the heart muscle If on the other hand physical exertion induces a quickened pulse which soon returns to its original rate or slower it shows that the weakened heart action is probably hypotonic in origin and susceptible of improvement under regulated exercise A pulsus paradoxus sometimes accompanies severe pericarditis

Pleurisy occurring in 5 to 10 per cent of patients, is more frequent on the left side when it usually accompanies pericarditis It generally indicates a severe rheumatic infection but occasionally is the chief evidence of a relapse in a patient who has had polyarthritis weeks or months before Rarely it is the initial manifestation of rheumatic fever and probably certain cases of so called idiopathic pleurisy are rheumatic in origin

The onset of pleurisy is heralded by intensification of the signs of general infection and by characteristic sharp stabbing pain on inspiration With the accumulation of fluid the pain decreases but tachypnea at first the result of pain becomes more accentuated, due to the compression of lung and often to a concomitantly weakened myocardium Pleural exudate, as a rule need not be aspirated but at times, with marked embarrassment of respiration *paracentesis pleurae* adds much to the patient s comfort

While the occurrence of a true rheumatic pneumonia is controversial there is found in many subjects postmortem a pulmonic consolidation containing many large cells resembling those of rheumatic granulomata Often these lesions are near areas of vasculitis Pneumonic signs are difficult to interpret clinically for the accompanying pleural effusions and pericardial exudates or a dilated heart give a mixed picture At times the onset of pneumonia is reflected by renewed signs of infection again it is discovered only in careful routine physical examinations or in roentgenograms Blood streaked purulent sputum suggests pneumonia

Upper Respiratory—Hemolytic streptococcal infection of the nose paranasal sinuses pharynx pharyngeal lymphatic tissue and tonsils is probably the most frequent single feature of rheumatic fever While the sequence of nasopharyngitis latent period and rheumatic symptoms is common the latent period may be so shortened that the first and third phases are almost simultaneous In patients with subacute rheumatism recrudescence is often preceded or accompanied by signs of renewed paranasal sinusitis and relieved by disappearance of this condition Many rheumatic subjects especially children have chronically diseased tonsils enlarged satellite cervical lymph nodes and persisting redness along the anterior faucial pillars signs more indicative of chronically infected tonsils than is simple enlargement of these organs Accompanying acute attacks of polyarthritis there are sometimes diffuse pharyngeal redness and discomfort and both arthritis and pharyngitis respond to antirheumatic drugs indicating that they are comparable processes Laryngitis the result of spreading pharyngitis is not infrequent occasionally discrete nodules appear on the vocal cords very rarely acute

edema of the epiglottis and vocal cords is encountered a very serious complication

Respiration—In all patients there is an increased respiratory rate parallel with the fever and quickened pulse, but dispropor tionately rapid breathing may accompany pneumonia pleurisy or carditis Tachypnea as a concomitant of rheumatic carditis is especially noticeable in children in whom the rate may be from 50 to 70 per minute without any evidence of pulmonary infec tion Attacks of rapid breathing in adults may accompany extensive severe poly arthritis and merely reflect the extreme pain the patient is suffering in such instances the relief of pain by splinting or anodynes is fol lowed by a decreased respiratory rate

The *cutaneous manifestations* of rheu matic fever consist of various exudative dermatoses but none is absolutely typical of the disease as similar rashes are seen in other infections and apparently as inde pendent conditions Various types of erythema multiforme are the most common often the rash starts as flat papules rapidly increasing in size, and clearing in the centers finally the migratory borders of several lesions fuse into an extensive marginate erythema Frequently the evolution and resolution occur within a few hours Often such rashes recur for weeks or months They commonly do not itch hence may be easily over looked Occasionally purpura is seen Whether the syndromes included under Henoch s purpura and Schönlein s disease are of rheumatic origin it is impossible at present to decide

Erythema nodosum is an occasional com plication sometimes there is only a single outbreak in other patients there are re peated crops of painful subcutaneous indu rated areas with the overlying skin at first red later purple and greenish

Sudaminal eruptions following the severe sweating are usual manifestations of a severe febrile intoxication

Subcutaneous nodules one of the most im portant of the rheumatic series indicate that the patient s response to the infection is chiefly proliferative in nature and wide spread in distribution with concurrent myo carditis and valvulitis hence their existence is considered of serious if not of fatal prog nostic import but many patients with them recover and return to a normal useful life for years Being usually painless they must be diagnosed by inspection and palpation over the extensor aspects of joints along the spine and over superficial flat bony surfaces such as the skull scapula olecranon patella and malleoli they may also be seen in super ficially located tendons and tendon sheaths They are best demonstrated by placing the patient between the light and the examiner and having the skin over the suspected area tightly stretched usually by flexing the joint They then appear as white or light gray nodules from 1 to 10 mm in diameter connected with the deep fibrous tissue and not with the skin which is freely movable over them Palpation reveals them as hard and only slightly movable when the joints are flexed somewhat more so when extended If in the scalp or over the bellies of muscles they must be detected by palpation but as a rule let it be emphasized they are best found by inspection Conglomerate masses are often seen Each nodule persists for from a few days to several weeks and although of rapid evolution it usually undergoes more gradual resolution Often they occur in suc cessive crops so that in a given area nodules of various ages may be found They appear while the patient is saturated with sodium salicylate or aminopyrine and unlike rheu matic arthritis do not disappear quickly when the patient is placed fully under the influence of these drugs

Blood Picture—Not infrequently a washed-out waxy appearance is seen in pa tients who have undergone severe or pro longed attacks this is due to a secondary anemia the degree of which can be defi nitely determined by hemoglobin estimations and erythrocyte counts

Leukocyte counts made at weekly to fort nightly intervals furnish useful indices of the progress of the infection With high fever and polyarthritis there is a leukocytosis of 15 000 to 25 000 which decreases with the diminution of symptoms either spontaneous or drug induced In the monocyclic infection the count returns to and remains normal after a few weeks In polycyclic and continu ous forms on the other hand there is usu ally though not always a low grade leuko cytosis increasing prior to or with a clinical relapse Even with the patient under drugs

there may be a low grade leukocytosis to indicate persisting infection

Erythrocyte Sedimentation Rate—This in general is a good index of rheumatic activity The usual technic is that of Westergren and only in the presence of considerable anemia are corrections required for this factor In acute stages rates of 100 to 130 mm per hour are found With improvement the rate drops in monocyclic cases steadily to normal in chronic cases rates of 30 to 60 are long maintained Rates above 20 probably indicate continued rest In patients with chorea the rate is often normal Abnormal E S R curves are generally better indications of rheumatic infection than is leukocytosis Both considered together are better than either alone Other causes for abnormal rates should be eliminated in weighing their significance Recently Schultz has found the *formol gel* reaction to be abnormal in cases of apparently active rheumatic carditis where the E S R was normal

Nervous Manifestations—Delirium followed by coma may accompany hyperpyrexia rheumatica With moderate fever delirium occasionally occurs and sometimes there are other acute psychoses which may become fixed enough to require special institutional care Large doses of salicylates sometimes induce delirium

Bruetsch has described a remarkable frequency of rheumatic valvular deformities among insane patients in whom there were often areas of cerebral degeneration apparently secondary to rheumatic involvement of the cerebral blood vessels He suggests that this disease is responsible for approximately 4 per cent of insanity

Chorea is now considered one of the important rheumatic manifestations Accompanying most fatal chorea there is typical rheumatic carditis In the simple uncomplicated form however chorea may be considered one of the mildest of the rheumatic series When on the other hand chorea accompanies or follows polyarthritis or carditis the type of rheumatic infection should be regarded as unusually severe and liable to be followed by permanent cardiac damage In any case therefore the existence of chorea indicates that the child is 'rheumatic and hence should be protected from unusual stress and strain and specially guarded against hemolytic streptococcal infections

Kidneys—Albuminuria and cylindruria running roughly parallel with the pyrexia are fairly common Goldring and Wyckoff noted a marked increase in erythrocytes and casts as detected by Addis counts and persisting for eight or ten weeks Similar abnormalities of shorter duration appear about the third week after simple tonsillitis and there is more severe renal involvement of a similar nature after scarlet fever Occasionally rheumatic fever is accompanied by a true hemorrhagic nephritis from which recovery is usually complete Some clinicians claim that many cases of idiopathic nephritis are merely instances of isolated rheumatic kidney disease Large doses of salicylates sometimes induce hematuria and an outpouring of small castlike bodies neocinchophen induces similar signs of irritation aminopyrine rarely does All anti rheumatic drugs apparently lower the renal threshold for nonprotein nitrogen hence fever dehydration and drugs favor the formation of a urine containing an excess of urates

Gastro-intestinal Tract—Instead of upper respiratory prodromata attacks of rheumatism are sometimes preceded by mild gastroenteritis and very occasionally by signs of appendicitis Indeed symptoms of appendicitis in rheumatic subjects often warrant delaying operation until the effect of anti rheumatic drugs has been tested Gastric symptoms may result from the rheumatic intoxication antirheumatic drugs or cardiac failure In the first and third instances relief will follow proper medication in the second a change of drugs is often useful

Nutrition—In all types of rheumatic fever the general nutrition of the patient suffers In the acute forms the weight drops rapidly with recovery it is regained quickly In the subacute and chronic disease while the loss may be more gradual it is often correspondingly difficult to repair The weight curve is therefore an important guide to the patient s condition Continually falling or remaining subnormal it indicates that he is not overcoming the infection a sudden drop often heralds a relapse A steadily rising curve is favorable but persistent low grade infection is seen even in overweight patients Those taking large amounts of antirheuma

tic drugs often show a marked drop in weight due to severe sweating Occasionally when these drugs are given to the point of distinct renal irritation there is a sharp increase in weight due to edema In addition to the increased destruction of vitamins incident to most infections rheumatic fever patients usually show a decreased vitamin A content of the blood 50 to 80 per cent below normal (Shanks Coburn and Hoagland)

Rheumatic fever in children, unless acutely fatal usually runs a subacute or chronic course Frequently the infection is so insidious both in its onset and manifestations that the true nature of the illness in the young is unrecognized until the characteristic symptoms appear In this prerheumatic state or subclinical rheumatism the soil is probably prepared for later more serious damage hence suspicion of its existence indicates the closest study The various types of manifestations shown by children —polyarthritis pleurisy carditis chronic tonsillitis growing pains chorea and subcutaneous nodules—have been designated as the rheumatic series In general the combination of acute toxic and exudative manifestations so characteristic of the infection in adults is less marked in children on the other hand chronic low grade intoxication together with focal proliferative lesions furnish the usual picture in the young Arthritis is less extensive and more transitory there is usually carditis relapses are common Each relapse may be made manifest by only one or two members of the rheumatic series but over the course of years the entire gamut may be run A careful record of temperature sleeping pulse rate cardiac signs electrocardiograms and erythrocyte sedimentation rates has shown that children have o called subclinical rheumatic relapses with a frequency previously unsuspected With each relapse there are increasing signs of cardiac damage and unless the resisting capacity of the patient can be made sufficient to throw off the infection permanently the final picture is one of cardiac failure

If on the other hand the child contracts no more hemolytic streptococcal infections and hence suffers no rheumatic recurrences he may recover without permanent cardiac damage or with valves so slightly deformed that their normal function is little compromised Indeed murmurs considered as arising from diseased valves may disappear later in life

Diagnosis —Although Group A hemolytic streptococci apparently play such an important etiologic role immune reactions tested with streptococcal products have no definitive diagnostic import in respect to rheumatic fever but are indicative of the precursory streptococcal invasion In doubtful cases their absence is presumptive evidence against the existence of rheumatic fever The positive diagnosis of this disease therefore still rests mainly upon careful and well documented clinical observations

Following scarlet fever all the signs of true rheumatic fever may occur this is especially true if the patient has had a previous attack of rheumatism Puerperal sepsis may likewise precede rheumatic fever Common hemolytic streptococcal etiologic factors probably are at work in all

The migratory polyarthritis responding to certain drugs is a feature practically unduplicated by other diseases Early signs of cardiac involvement subcutaneous fibroid nodules persistent undernutrition low grade toxic state and concomitant chorea are all important aids in arriving at a correct diagnosis

Many infectious diseases are occasionally complicated by arthritis The antecedent history and positive evidence of the persistence of a specific infection are therefore important in determining the cause of a secondary arthritis In most purulent arthritides the causative micro organism is demonstrable in aspirated synovial fluid and immediate microscopic examination will at times settle the diagnosis At other times one must await the results of cultures Patients with gonorrheal rheumatism often have migratory serous polyarthritis but eventually one or two joints become persistently involved with a boggy edema and gonococci can usually be grown from the aspirated purulent synovial fluid if proper culture media are employed A history of gonorrhea the demonstration of gonococci in the genitourinary tract and of complement binding antibodies in the blood serum are important differential points Rapid disappearance of symptoms and signs of arthri

tis usually follow adequate doses of the *sulfonamides*

About half of the patients with undulant fever have arthritis involving principally the shoulders hips and knees Other features of the disease and demonstration of agglutinins and opsonins in the blood serum for Brucella confirm the diagnosis

In children acute septic arthritis and osteomyelitis may be mistaken for rheumatism Diagnosis is made by the extremely toxic state of the patient bogginess of the joint purulent character of the aspirated fluid and demonstration of staphylococci or streptococci in the synovial fluid and blood Hemophilia and scurvy in children also lead to painful swelling of the joints the nature of which should be determined from other features of these diseases

A subacute to chronic low grade polyarthritis with little if any demonstrable effusion is not infrequent following attacks of bacillary dysentery Whether sulfaguanidine will favorably affect this complication is as yet unknown

Rheumatoid arthritis or chronic secondary infectious arthritis sometimes begins acutely with features closely resembling rheumatic fever The initial and persistent involvement of small joints of the hands feet and spine and the comparative freedom from cardiac complications are suggestive features The persistence of periarticular swelling leading to obvious deformity confirms the diagnosis

Acute gout must sometimes be considered Family and personal history the deposits of tophi in the ears and of urates about the joints and the almost pathognomonic x ray picture of the bones should clear up any doubt A high uric acid content in the blood is very suggestive and a disappearance of the arthritis under adequate doses of colchicine is diagnostic

Polyarthritis is one of the most striking symptoms of serum disease following antitoxic or antibacterial serum therapy Marked pain and stiffness of the joints with very slight if any effusion absence of periarticular swelling and redness a coexistent urticaria and the history of serum treatment within a period of ten to twenty days serve to determine the nature of the trouble

Prognosis—This covers two phases The acute attack and the rheumatic heart disease The mortality from the first varies between 1 and 4 per cent and is practically always due to acute carditis occasionally accompanied by hyperpyrexia which is an ominous manifestation About puberty many children with badly damaged hearts succumb apparently because the hypertrophied organs cannot respond further to the rapid body growth With puberty however many patients develop some unknown type of resistance so that rheumatic recurrences are much less frequent than in childhood Indeed in each decade of life the liability to contract the disease and to develop permanent cardiac damage diminishes Chorea alone indicates a mild infection but chorea or subcutaneous nodules increase the gravity of the outlook Subcutaneous nodules are indicative of cardiac involvement but not necessarily fatal In general severe acute attacks damage the heart more than mild ones and polycyclic and continuous courses more than monocyclic Pericarditis indicates a severe pancardiac involvement

Several statistical studies indicate that the average life of patients with definite rheumatic heart disease is thirteen to fifteen years with shorter average duration for those who first developed the disease in childhood The ultimate prognosis is somewhat proportional to the severity of the cardiac damage and to the frequency of recurrence of attacks of rheumatic fever A patient who has suffered one attack of the *disease is three or four times more* liable to have rheumatism again if he contracts a streptococcal infection than is one who has never had rheumatism hence the importance in ultimate outcome of the prevention of streptococcal infections either by living under a better environment or by chemoprophylaxis

Treatment—Most important is the understanding by the physician of the nature of the malady and the action of the therapeutic agents This is particularly true with rheumatic fever because of the different clinical types protean manifestations implication of important viscera and the existence of drugs favorably *influencing* symptoms without eliminating the causative agent Systematic documenting of the various features is most helpful in picturing the

course of the infection, the importance of recognizing this cannot be overemphasized for it is obviously more reprehensible to allow a patient with active carditis to exercise too soon than to keep him inactive too long If significant records of these patients were kept we would hear less often 'The patient recovered two months ago from rheumatism but now is suffering from endocarditis

Rest relief of pain attention to nutrition and regulated convalescence are the chief therapeutic indications With acute polyarthritis rest is enforced by pain when pain disappears rest must be insisted upon by the physician While fresh air is beneficial the patient should be guarded from chilling which easily occurs because of the severe perspiration requiring frequent changes of the bed linen and patient s clothing Frequent bathing and dusting with some absorbent powder helps to prevent maceration of the skin Swathing the affected joints with flat pads made of cotton covered with gauze affords much comfort The support of the limbs by pillows so placed as partially to flex the joints provides the most comfortable position

Large amounts of fluid should be given to encourage the elimination of toxic substances and to replace water lost in sweating A high caloric diet composed of easily assimilable food should be provided often it is necessary to cater to the patient s taste in order to maintain nutrition During convalescence it can be coarser and more varied than at the time of high fever During the acute phases at least double the basic amount of the vitamin B complex and vitamin C should be furnished and probably three or four times the usual requirement of vitamin A

Drug Treatment —Practically all of the acute distressing symptoms except those due to cardiac failure are relieved by the *compounds of salicylic acid* These act as antipyretics and analgesics when given properly The therapeutic and toxic doses are close together hence the attendants should watch for the first symptoms of salicyl intoxication These are ringing in the ears deafness nausea vomiting and rarely delirium renal irritation must be detected by examination of the urine Sodium salicylate dissolved in water or in capsules or acetylsalicylic acid (aspirin) should be given in doses of 1 to 1.3 Gm (15–20 grains) every hour for from 8 to 10 doses or discontinued sooner if toxic symptoms appear The next day three fourths of the determined toxic dose may be given and following this the drug continued at about the same rate It should be continued until all signs of active infection have been absent for a week or ten days If well tolerated it should then be decreased gradually with constant watch for symptoms of relapse If these recur the dose must be increased The administration of sodium bicarbonate with salicylates is mainly to prevent gastric irritation but the bicarbonate should not be given in doses large enough to induce alkalosis Acetylsalicylic acid (aspirin) tablets are very irritating to an empty stomach much less so to one containing food The rectal administration of 120 to 180 cc of 2 per cent solution of sodium salicylate (10 grains to 1 ounce of water) two or three times daily is sometimes well tolerated when the drug given by mouth leads to nausea If rectal irritation results a weak starch solution as a vehicle may be substituted for the water Intravenous administration of salicylates has no special advantage

Neocinchophen once widely recommended has no special merit over the salicylates and is much more expensive

Aminopyrine (pyramidon) has antirheumatic effects similar to those of salicylates and acts more promptly in smaller doses It usually has few if any toxic side actions hence is specially useful in the presence of gastric irritability especially that due to heart failure from very active rheumatic carditis Its capacity to induce agranulocytosis occasionally makes it necessary to do fairly frequent leukocyte counts If the white blood cells drop to 4000 or 5000 per c mm the aminopyrine should be immediately stopped Probably agranulocytosis occurs in subjects with an idiosyncrasy to this drug and is more frequent in older persons with wasting diseases than in the young Aminopyrine is given in doses of 0 3 to 0.5 Gm (5 to 7 5 grains) four to six times daily with some doses during the night The total dosage should be sufficient to control the acute attack and after this

end has been attained the dosage may be reduced to a point just above that necessary to control the symptoms

Antistreptococcal Drugs—The sulfonamides so useful in many acute hemolytic streptococcal infections do not favorably influence the course of established rheumatic fever Sulfanilamide in fact, eems to aggravate the rheumatic symptoms The prophylactic action of these drugs is discussed later

Morphine or *codeine* is sometimes required to control pain especially thoracic

Digitalis should be given for heart failure as soon as signs of this appear Auricular fibrillation with active carditis usually calls for this drug as does a continuous cardiac rate of 130 or more A standardized preparation should be employed and therapeutic digitalization should be attained by giving 4 cat units the first dose 2 units after four to six hours and 2 units the next day if signs of overdigitalization are absent Maintenance dosage consists of ½ to 1½ cat units occasionally more per day Signs of overdigitalization are nausea vomiting extrasystoles especially in coupled beats Not infrequently both antipyretic drugs and digitalis are required to render comfortable a patient with active carditis

The treatment of complications follows symptomatic indications Severe precordial pain can often be alleviated by a light icebag over the painful area at other times heat furnishes more relief If the heart s action is much embarrassed by excessive pericardial exudate removal of the fluid sometimes is useful but as a rule this fluid is absorbed spontaneously Likewise it is necessary to remove pleural fluid only when the breathing space is much diminished

Serum Treatment—The parenteral injection of antistreptococcal horse or beef serum has been not only useless but at times has given rise to increased fever tachycardia dyspnea cyanosis and pulmonary congestion occasionally to severe arthritis Possibly a specific serum of the type homologous to the streptococcus infecting the patient might effect a cure but there are no therapeutic trials of this nature There is no convincing evidence that the serum of patients who have recovered from rheumatic fever has any beneficial effect

Nonspecific Shock and Fever Therapy—Some observers have noted a rapid recovery following various forms of nonspecific shock treatment L P Sutton noted rapid recovery from chorea following intravenous injections of typhoid vaccines and later showed that the beneficial effect was due to high fever which could be induced in hot boxes heated with carbon filament lamps or in a Kettering apparatus Some suggestive improvement following heat therapy was also recorded in patients with chronic carditis or subcutaneous nodules

Intravenous Vaccination with Streptococcal Vaccines—This treatment was based on the hypothesis that part of the rheumatic manifestations were due to a hypersensitive state of the patients tissues to streptococcal products and also on the observations that rabbits with induced hypersensitivity to streptococci could be best rendered hyposensitive by intravenous immunization In acute rheumatism both focal and general reactions induced by relatively small amounts of these vaccines can be prevented by antirheumatic drugs and the patients can be made tolerant to many times the original symptom inducing dose by suitable intravenous vaccination In animals it was later shown that such desensitization was closely related to the type specificity of the streptococci employed to sensitize them As many types of Group A streptococci cause the disease precursory to the rheumatic fever the entire subject of immunization and desensitization of rheumatic subjects must be restudied

Convalescence—During this period the greatest care must be exercised The rate of recovery is roughly proportional to the length and severity of illness The patient should remain in bed until free from fever and other signs of infection for two or three weeks without being under the influence of antipyretics The weight should have returned to normal the heart rate be fairly slow leukocytosis should be absent and the erythrocyte sedimentation rate should be below 15 to 20 The period of sitting in a chair should be slowly increased until he can sit up four or five hours a day without undue fatigue or reawakening the infection Then walking may be permitted a few steps at first then gradually increased Stair

climbing should not be permitted until walking on the level can be done without undue reaction A good guide to the effect of exertion is gained by noting the pulse rate immediately before exercise, immediately after and five minutes later if it is then not increased over the original rate increased exertion may be permitted if it is more rapid exercise should be diminished Reappearing signs of infection demand a return to complete rest The principles to follow are the physical retraining of a person whose heart has probably been diseased and in whom reinfection may cause further cardiac damage

Prophylaxis —As a guiding principle it now seems safe to assume that the prevention of Group A hemolytic streptococcal infections will prevent rheumatic fever While the practical attainment of the first leaves much to be desired still something may be accomplished by intelligently aimed efforts As the degree of progressive rheumatic heart disease is roughly proportional to the number and severity of recurrences of rheumatic fever prophylactic efforts are justifiable

A person who has recovered from rheumatic fever should avoid contact with patients having streptococcal infections and should be removed from such an environment The common use of dishes towels or other possibly contaminated objects should be avoided and the nature of air borne infections should be kept in mind Where it is possible to move a specially susceptible rheumatic subject to a southern climate this may be of value provided that environment insured freedom from exposure to streptococci otherwise it is of little value

Chemoprophylaxis —A patient with an acute hemolytic streptococcal infection treated with sulfonamides may develop rheumatic fever On the other hand there is now convincing evidence that they are efficient prophylactic agents of hemolytic streptococcal infections and when such infections are effectively prevented in previously rheumatic subjects there are no rheumatic recurrences The usual procedure has been to administer sulfanilamide daily in doses of 1 to 2 Gm from September to June the season of greatest danger and to maintain a blood level of 1 5 to 2 0 mg per cent While sulfathiazole and sulfadiazine have been used to a less extent they appear to have a similar prophylactic action and the latter may be the drug of choice because of lower toxicity The toxic by effects of these drugs make necessary their discontinuance in some cases All patients under going such chemoprophylaxis must be constantly under observation and have regular blood counts and urine examinations Any persistent toxic effect is an indication for stopping the drug

It has been suggested that continued administration of salicylates to a patient with a streptococcal infection might prevent an attack of rheumatic fever While there is little doubt that symptoms of rheumatism might be prevented just as they are alleviated after appearing there is as yet no satisfactory evidence of the suppression of a true rheumatic recurrence

Tonsillectomy —Our modern concept of the etiologic role of streptococcal infections gives us a more rational attitude towards the prophylactic effect of tonsillectomy The removal of tonsils may diminish a person s chances of acquiring such an infection but the fact that a very slight streptococcal infection of the nasopharynx may induce a rheumatic recurrence shows how ineffective a tonsillectomy may be in this respect There is still much lymphoid tissue left in the naso and oropharynx to harbor streptococci The question of tonsillectomy should therefore be considered from the standpoint of the patient s general health and its bearing on the rheumatic process and not on the rheumatic process alone Tonsils should not be removed during the acute phases of rheumatic fever, and prior to tonsillectomy a rheumatic subject should be given some sulfonamide preferably sulfadiazine to kill off any microorganisms that might enter the blood stream during the operation

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THE ERYTHEMAS

Definition —The term erythema signifies a blushing This heading covers a somewhat indefinite group of diseases in which the essential clinical picture is a redness or hyperemia of the skin

The lesions of the erythemas assume various forms They may occur as either a localized or a generalized blushing of the cutaneous surface or as a number of more or less circumscribed areas of hyperemia sometimes with raised surfaces and sometimes in patterns In generalized erythema the face trunk upper arms and thighs are more frequently involved than other parts of the body

Etiology —*External Causes* —The erythemas due to external causes are generally confined to areas of the body directly exposed to an irritant These irritants are either physical or chemical in nature Among the physical are friction pressure heat sunlight roentgen rays and radium among the chemical are acids alkalis turpentine mustard insect stings poisons of plants and septic discharges Skin conditions caused by the poisons of plants are generally designated as *erythema venenatum*

Internal Causes —One of the most frequent causes of erythema is hypersensitiveness to certain foods particularly shellfish and berries Drugs such as atropine chloral hydrate quinine sodium salicylate and mercury occasionally produce an erythema in patients with an idiosyncrasy to them *Erythema medicamentosum* is a name sometimes applied to an erythema caused by drugs Bacterial toxins injected serum and toxic products absorbed from the gastrointestinal tract may also produce an erythema

Pathology —The histologic feature of prime importance is dilatation of the capillaries In some cases there may be also an exudation of serum leukocytes or even of red blood cells into the surrounding tissue

Signs and Symptoms —Hyperemia as evidenced by redness of the skin is the most important finding in erythema In this condition the color disappears on pressure and reappears when the pressure is withdrawn Tenderness a burning sensation and itching are often present A severe erythema is frequently followed by desquamation and pigmentation The eruption is generally of short duration

Constitutional symptoms such as fever and malaise are either entirely absent or very mild

Diagnosis —Erythema due to external causes is generally recognized by a history of exposure to some skin irritant Erythema due to internal causes is sometimes more difficult to diagnose although a history of having taken some drug or particular food to which the patient has an idiosyncrasy or a history of infection, or of a gastrointestinal disorder may serve as a clue to the nature of the condition

Lack of constitutional symptoms is an important feature in making a diagnosis of erythema

Treatment —The most efficacious treatment for erythema consists in recognizing its cause and treating that Local irritation may be relieved by the application of a simple dusting powder or by sponging the skin with a weak solution of sodium bicarbonate alcohol or boric acid in water Analgesics such as sodium salicylate or acetylsalicylic acid are sometimes indicated and rest in bed is generally advisable The use of soaps and other substances irritating to the skin should be discontinued

Several forms of erythema are worthy of mention

W J STAINSBY

ERYTHEMA MULTIFORME
(*Erythema Exudativum Multiforme*)

Erythema multiforme as the name implies is distinguished by the varied aspects of its lesions—two cases seldom being alike The eruption may be macular papular circinate bullous or hemorrhagic As a rule it is symmetrically bilateral with a predilection for the face neck arms legs and dorsal surfaces of the hands and feet Mucous membranes may also be involved In the past a host of names such as erythema papulatum and erythema annulare have been employed to designate different types of this disease An elaborate classification serves no useful purpose and merely tends to confuse rather than to clarify the subject as the etiology distribution of the eruption and course of the disease are similar regardless of the type of the lesion

Symptoms —In erythema multiforme constitutional symptoms are either entirely absent or are very mild varying somewhat with the underlying processes In some cases there is a mild fever and in a few malaise The pathologic picture is similar to that already described under erythema

Etiology —The etiology of erythema multiforme is unknown—some investigators associate it with foci of infection in the teeth tonsils sinuses or uterus while others associate it with the absorption of toxic products from ingested foods The disease is known to be particularly prevalent in the spring and autumn which is sometimes thought to indicate that dampness and rain or changing temperatures play a part in its etiology

Prognosis —Erythema multiforme as a rule runs a course of a few days to two or three weeks Rarely it may last for several months Some patients have a recurrence every spring or every spring and autumn

Diagnosis —Erythema multiforme must be differentiated from the maculopapular syphilide and from ringworm pityriasis rosea pemphigus dermatitis herpetiformis and lupus erythematosus Erythema multiforme is distinguished by its comparatively short duration and the absence of any tendency to form adherent scales or to permanently injure the skin

Treatment —The treatment for erythema multiforme is similar to that already described under erythema Attempts should be made to determine its etiology if possible and by correcting that to eradicate the condition

W J STAINSBY

ERYTHEMA NODOSUM

The eruption erythema nodosum consists of poorly defined nodular lesions varying in diameter from a few millimeters to 5 or 6 cm The lesions are prone to appear on the shins but may occur on any of the extremities or on the buttocks The skin over the nodules is smooth shiny and generally of a rose-red color Ulceration seldom takes place The nodules appear in crops last from a few days to several weeks and slowly disappear

In erythema nodosum the eruption is usually preceded by mild constitutional symptoms such as fever malaise and pain in the muscles and joints, and is sometimes accompanied by definite polyarthritis

Etiology —Erythema nodosum does not have a specific etiology and it is now generally considered that almost any infectious disease may produce the condition The outstanding sources are rheumatic fever tuberculosis syphilis and infections caused by the gonococcus and meningococcus

Histologic examination of lesions of this disease show that there is dilatation of the capillaries and extravasation of serum leukocytes and erythrocytes into the surrounding tissues The bruised appearance which the lesions assume on healing is due to the disintegration of red blood cells

Treatment —In the treatment of erythema nodosum emphasis should be placed on an effort to determine the etiologic factors underlying the condition and to correct or remove them Analgesics especially salicylates are useful when the eruption is accompanied by pain Soothing lotions as previously described may be applied locally

W J STAINSBY

ERYTHEMA INFECTIOSUM

Erythema infectiosum is a mildly contagious disease that produces a generalized erythema of the cutaneous surface that often

varies in appearance with individual cases but which when typical is characteristic of the disease The condition begins insidiously with a dusky flushing of the cheeks which is soon followed by a generalized erythema which is more marked on the buttocks and extremities than elsewhere Associated with the erythema there are always more or less well defined macular and papular lesions The generalized erythema lasts for several days to a week when the lesions disappear from the trunk but persist for an additional week or more on the arms and the legs

When the lesions on the arms are well defined, no mistake can be made as to the nature of the condition The rash starts there as a small area of erythema with a sharply defined edge that gradually spreads peripherally clearing up completely in the older parts of the lesion When an area such as this coalesces with other areas developing in the same manner one sees an arm that is covered with irregular serpiginous lines winding about the arm and surrounding small areas of normal appearing skin

There are no generalized symptoms other than slight malaise and sometimes mild tickling or burning of the skin The disease is uncommon

Etiology —The infecting agent is unknown and the incubative period is from four to fourteen days

Differential Diagnosis —Erythema infectiosum must be differentiated especially from rubella measles and scarlet fever This can usually be done by the characteristic appearance of the rash particularly on the arms and the almost complete absence of symptoms other than those produced by the skin lesions

Treatment —None is indicated No fatalities have been reported Isolation aids in preventing a spread of the condition but the disease is so mild that insistence on such a course is unnecessary

W J Stainsby

ERYTHEMA INDURATUM

(Bazin s Disease)

Erythema induratum appears as a localized red or violet discoloration of the skin that gradually turns brown Associated with the color changes there develop in the cutis or subcutaneous tissues freely movable nodules that may vary in size from a few millimeters to several centimeters in diameter The nodules sometimes ulcerate leaving shallow craters covered with a serous rather than a purulent exudate These ulcers are regular in outline and their edges are not undermined The condition is usually bilateral with a predilection for the calves of the legs, although the face, trunk and arms are sometimes sites of the lesions Females are much more frequently affected than males

Etiology —Erythema induratum is caused by the tubercle bacillus but it must be remembered that syphilis and leprosy can produce similar clinical pictures

Treatment —Treatment consists of rest of the part affected, elevation of the extremity, and localized support by means of bandages The disease tends to heal slowly but scarring usually results

W J Stainsby

ERYTHEMA OF THE NINTH DAY

Erythema of the ninth day is a term applied to a generalized erythema that occasionally occurs following the administration of arsphenamine or neoarsphenamine More recently reports have appeared in the literature which indicate that this condition can develop following the intramuscular injection of bismuth It occurs from eight to ten days following the injection of the drug with an average of nine days from which the term is derived It is a self limited mild reaction and the nature of the condition is not clearly understood Recognition of the symptom complex is important so that it will not be confused with the more serious arsenical dermatitis

Treatment —Usually none is required The condition remains only a short time and is definitely self limited Arsenicals may again be injected as soon as the rash has cleared

W J Stainsby

SARCOID OF DARIER ROUSSY

This type of sarcoid differs from Boeck's sarcoid in that the lesion lies chiefly in the

subcutis rather than in the cutis There is an infiltrative thickening of the skin and subcutaneous tissues and the color varies from that of normal skin to a pinkish or rose color Nodules varying in size up to 2 cm in diameter appear and are located in the subcutaneous structures and tend to arrange themselves in columns or strings While any part of the body may be involved the disease tends to attack the trunk particularly the buttocks

Histology —The lesion is made up of areas of epithelioid cells which lie in the subcutis with strands radiating to the cutis and fatty tissues Along with the epithelioid cells are a varying amount of connective tissue *lymphocytes and giant cells*

Etiology —The etiology is not definitely established but the tubercle bacillus has been suspected as an etiologic agent by several investigators of the disease

Treatment —X ray therapy may be tried and some patients have been benefited by this form of treatment

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SARCOIDOSIS

(Boeck s sarcoid Lupus pernio Benignes Miliar lupoid Benign lymphogranulomatosis Osteitis tuberculosa multiplex cystoides Mortimer s malady Hutchinson Boeck s disease Maladie de Besnier Boeck Besnier Tenneson s disease Schaumann s disease Uveoparotid fever or Heerfordt s disease)

Definition —Sarcoidosis is a chronic indolent and benign infectious disease of unknown cause involving the skin lymph nodes eyes salivary glands lungs and bones of the hands and feet especially In addition to these conspicuous lesions disseminated systemic manifestations bespeak widespread pathological changes The predominance of certain lesions has perpetuated as clinical entities such groupings of clinical details as uveoparotid fever

Etiology —Tuberculosis has been cited as the underlying cause of sarcoidosis by most observers Acid fast organisms have at times been seen in the lesions but Koch s postulates have not been fulfilled in any further detail Furthermore the reactions to large doses of old tuberculin are conspicuously feeble or negative Singularly the lesions of sarcoidosis disappear upon the development of active tuberculosis Some maintain that the products of the *Mycobacterium tuberculosis* rather than the organism itself may be responsible for the disease

The *Mycobacterium leprae* has received some attention in this connection The difficulty in cultivating the acid fast bacilli from the sarcoid lesions and in reproducing the disease might well raise this question but with certain similarities in the cutaneous and bony manifestations of the two diseases the clinical resemblance ceases A filtrable virus has been incriminated on the basis of a Frei reaction following the intracutaneous injection of an emulsion of a sarcoid nodule into an affected subject Obviously further support must be marshalled before admitting such evidence for a virus etiology

Sarcoidosis may occur at any period of life but usually in patients between fifteen and forty years of age The rare occurrence of this disease in siblings does not favor a familial or a communicable basis Sex exerts no influence In this country there is an apparent predilection for the Negro but no race is exempt from its inroads Sarcoidosis appears more commonly in rural than in urban dwellers Most instances of the disease have been reported from the north temperate zone especially in Scandinavia northern Europe England and North America

Morbid Anatomy —The fundamental

lesion is granulomatous Large pale epithelioid cells are collected in isolated nests or well defined nodules As a rule, these areas are not sharply demarcated from normal tissue Occasional pale multinucleated giant cells complete the picture Neither necrosis nor caseation is observed The sluggishness of the process is significant Months may pass without perceptible histologic change In its natural evolution fibrosis may be anticipated These lesions have been found in the skin breast mucous membrane salivary gland lachrymal gland lymph node tonsil eye nervous system pituitary body, thyroid gland heart lung serous membrane *liver intestine spleen kidney, endometrium* prostate testis, epididymis voluntary muscle tendon sheath and bone The bone marrow and the Haversian canals have been found infiltrated by the characteristic epithelioid cells in sarcoidosis

Pathologic Physiology —The manifestations of disturbed function may be as wide spread as the lesions of sarcoidosis Xerostomia may attend the active phase of the uveoparotid syndrome but permanent alteration of salivary function is rare Visual disorders in this syndrome may be persistent and occasionally permanent difficulties even as serious as blindness may result Invasion of the pituitary body has given rise to diabetes insipidus Myxedema may arise from thyroid involvement Extensive pulmonary sarcoidosis may lead to polycythemia right heart strain and overstrain (chronic *cor pulmonale*) Tachycardia arrhythmia and heart failure have been attributed to cardiac invasion by this process The hyperglobulinemia may reflect the hepatic phase of the disease Renal involvement rarely advances to the degree of frank uremia but altered glomerular function is indicated by occasional albuminuria and hematuria Eunuchoidism may attend testicular encroachment

Symptoms —The patient suffering from sarcoidosis experiences slight constitutional reaction as a rule Fever is unusual Even major degrees of pulmonary involvement may occur without any accession of temperature Mild malaise and indisposition may appear Distaste for food vague gastric symptoms and diarrhea occasionally supervene Night sweats and arthralgia have been noted So insidious may be the onset that only the cutaneous eruption or the lymph adenopathy arouses clinical suspicion as to the true state of affairs The skin lesions appear in about 50 per cent of patients with sarcoidosis Boeck's description of three characteristic eruptions still pertains (1) Small firm cutaneous nodules (klein knotige) may be noted in the butterfly area of the face on the arms and back These nodules are sharply demarcated smooth brown or blue (2) Similar but larger nodules (grossknotige) may appear (3) The skin may be diffusely infiltrated and thickened (Lupus pernio) over the nose face and ears The tense skin over the affected *area* may be bluish but tiny yellow granules appear at the margins This eruption is not painful nor attended by pruritus Having reached its peak there may be no change for months Atrophic scars may mark the sites of earlier lesions but ulceration never occurs The mucous membranes of the nose and oropharynx may be reddened and nodular

The *involvement* of the *hands* serves as a clue to the diagnosis Firm nodules appear at the interphalangeal joints These may present a remarkable symmetry A knotty appearance may be imparted to the affected fingers and hands Scaling of the skin occurs over these projections The subject complains of tightness or stiffness of the fingers but they are not painful or tender General lymphadenopathy may early attract the attention Pre- and post auricular involvement is particularly significant The cervical submaxillary axillary epitrochlear and inguinal nodes may be involved As a rule the individual nodes are not especially large but there are exceptions These nodes are firm in consistency discrete and non tender Pressure symptoms rarely arise from them Cough dyspnea and remittent low grade fever may attend mediastinal or pulmonary involvement but extensive intrathoracic invasion may occur without significant subjective or objective evidence Interscapular dulness and bronchial breath sounds are occasionally elicited At times the pulmonary process may be so extensive as to lead to right heart embarrassment Hepatomegaly and splenomegaly may arise from sarcoid involvement of these organs

Uveoparotid fever constitutes an expres

sion of sarcoidosis requiring especial attention Insidiously as in the commoner forms of sarcoidosis the picture is evolved after non specific prodromes of lassitude drowsiness malaise and indefinite gastro intestinal symptoms Intermittent pyrexia of moderate degree may attend Firm painless swelling of the parotid glands usually precedes ocular involvement Although bilateral in a vast majority the invasion of the parotid glands is not simultaneous Dryness of the mouth may be a distressing symptom Mastication is not embarrassed by the parotid swelling The induration of the glands may be permanent Occasionally the ophthalmic symptoms anticipate the parotitis Uveitis is the most common detail of this picture but there have also occurred conjunctivitis corneal herpes keratitis corneal opacities vitreous hemorrhage optic neuritis neuroretinitis chorioretinitis glaucoma aqueous turbidity and cataract Relapses are not infrequent The third component in the uveoparotid syndrome is the cranial nerve involvement A majority of these patients develops seventh nerve paralysis unilateral or bilateral quite suddenly a few days to a few months after the onset of the parotitis The lower facial distribution is more involved than the upper Usually the facial palsy subsides *pari passu* with the parotitis but it may appear after its subsidence Occasional neurologic involvement of different orders may be observed such as paralysis of the soft palate dysphagia intercostal neuralgia paralysis of the vocal cords deafness ptosis of the eyelid wasting of the muscles of the hand loss of vibratory perception in the legs and polyneuritis

A slight hypochromic microcytic anemia may be anticipated in sarcoidosis The leukocytes are normal in number or there may be a slight leukopenia Monocytosis prevails Eosinophilia of a slight to moderate degree (up to 35 per cent) may occur in a minority Increased sedimentation speed is the rule The Wassermann reaction is negative The blood calcium and phosphatase are quite regularly increased and the blood phosphorus and cholesterol normal The total plasma proteins are increased largely by reason of the increase in the plasma globulin The albumin/globulin ratio is frequently reversed In the uveoparotid syndrome there may be added pleocytosis and increased protein in the cerebrospinal fluid The x rays of the chest may disclose two fundamental types of intrathoracic involvement Tracheobronchial and mediastinal lymphadenopathy may assume varying proportions From the hilum there may occur an extension along the peribronchial structures to involve the lung in an advancing process of fibrosis that fades centrifugally Patches of fibrous density may be scattered irregularly through the lung These changes are most marked at the bases In the second type of pulmonary sarcoidosis a reticular appearance is lent to the whole lung field and tiny densities stud the same to indicate a miliary distribution of the pathologic process Particularly significant is the x ray appearance of the shafts of the phalanges and metacarpal bones Without periosteal involvement or thickening rarefaction of the medullary portion of these bones takes place Eventually small punched-out areas appear in the small bones of the hands and feet (ostitis tuberculosa multiplex cystoides) Less commonly the long bones of the arms and legs are involved Sarcoidosis of the skull has been reported The bony changes are more extensive than are disclosed by the x ray Biopsies of the sarcoid lesions of the skin parotid tonsil and bone marrow are recommended in a diagnostic survey but the tonsil is not so regularly the seat of the pathologic changes as was once thought

Diagnosis—The diagnosis of sarcoidosis is usually made from the nature of the cutaneous eruption and the lymphadenopathy with or without the support of x rays of the thorax and hands Hutchinson s description of the skin lesions is significant in this relation The disease is characterized by the formation of multiple raised dusky red patches which have no tendency to inflame or ulcerate They are very persistent and extend but slowly They occur in groups their bilateral symmetry and the absence of all tendency to ulcerate or form crusts are features which separate the malady from lupus vulgaris To none of the other forms of lupus has the malady any resemblance' The uveoparotid syndrome adds the parotid tumor uveal tract involvement and facial palsy Invasion of the lachrymal and salivary glands may satisfy the diagnostic cri

teria of Mikulicz s syndrome Only blood studies and biopsy of the affected structures will properly catalogue its several origins General lymphadenopathy and splenomegaly may lead to the suspicion of Hodgkin's disease or hyperplastic tuberculosis The singular absence of constitutional symptoms and the sluggish course in sarcoidosis contrast to the rule in Hodgkin s disease and tuberculosis The degree and order of the pulmonary involvement upon x ray study contrast strikingly with the clinical well being of the patient with sarcoidosis This circumstance alone militates against the diagnosis of Hodgkin's disease and tuberculosis The negative Mantoux reaction and persistently negative sputa would be further evidence against a tuberculous explanation X ray of the hands should give the clue in a considerable proportion of the doubtful diagnoses The absence of periosteal change would rule out syphilis as well as tuberculosis The negative Wassermann reaction would be helpful The virtual absence of constitutional symptoms and the benign course exclude leprosy The industrial history might afford the answer to a possible confusion with silicosis Biopsy of accessible lesions would arbitrarily rule out Hodgkin's disease and lymphosarcoma but there might be raised the question of tuberculosis which may be met as stated Although the differences between tuberculous or syphilitic iridocyclitis and the uveitis of uveoparotid fever may be finely drawn parotitis and facial palsy are peculiar to the latter Furthermore a positive Mantoux reaction on one hand or a positive Wassermann reaction on the other would establish the respective etiologies

As the diagnostic horizon is lifted an extension of sarcoidosis to include a number of systemic disorders such as regional ileitis may increase the problem

Prognosis.—Although interrupted by relapses the course of sarcoidosis is singularly benign and free from grave constitutional symptoms Spontaneous recovery may be anticipated in a majority of these patients The pathologic lesions tend to heal by fibrosis Atrophic scars may mark obsolete cutaneous eruptions The lymph nodes become more dense Although the symptoms of the uveoparotid syndrome usually disappear entirely some induration of the parotid gland and more or less serious visual disturbances may persist The pulmonary changes may lead to chronic *cor pulmonale* with congestive failure Approximately 10 per cent of these patients develop clinical tuberculosis Clinical abatement of cutaneous sarcoidosis has attended activation of pulmonary tuberculosis In the occasional instance of invasion of some important structure such as the pituitary body thyroid gland or heart by the granulomatous process replacement of essential parenchyma may determine serious collateral effects A mortality of 5 per cent is reported

Treatment—The therapy of a disease with such a natural history is difficult to evaluate No specific has been reported Tuberculin is no longer advocated in the treatment of sarcoidosis Arsenic has no established place although an occasional success has attended the use of neoarsphenamine Gold therapy is not recommended The earlier promise of ultraviolet rays has not been generally sustained but the lymphadenopathy may recede under its application X ray and radium therapy offer nothing Antileprol (a derivative of chaulmoogra) was once acclaimed but has fallen into disuse General hygienic measures alone prevail at the present time Since neither infectivity nor for that matter tuberculous etiology has been established sanatorium treatment should be discouraged

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DISSEMINATED LUPUS ERYTHEMATOSUS

Definition—Among the heterogeneous group of so called rheumatoid diseases disseminated lupus erythematosus constitutes a disease entity distinguished by a prolonged clinical course which usually terminates fatally by a striking predilection for young females and by characteristic pathologic changes in the vascular system Because in many instances an erythematous rash is apt to appear on the face and other parts of the body at some stage of the disease the condition was first described about the middle of the nineteenth century by dermatologists (Hebra Casenave Kaposi) who named it lupus erythematodes or erythematosus In spite of its name this disease bears no relationship whatever to tuberculosis and lupus vulgaris nor to that benign indolent skin lesion known to dermatologists as discoid lupus

In recent years it has been recognized that the skin rash is not invariably present and that when it appears it is a superficial manifestation of a widespread injury to the collagen which serves as a matrix and binding substance for capillaries and other small blood vessels in various parts of the body The appearance of an erythema spreading in a butterfly pattern across the bridge of the nose and the malar eminences in a patient suffering from fever and the other systemic manifestations of this disease greatly facilitates the diagnosis But even in the absence of the rash the characteristic combination of other clinical manifestations should be adequate for the diagnosis On the other hand an erythema on the bridge of the nose and the malar eminences may be due to a variety of other causes and it alone does not warrant a diagnosis of disseminated lupus erythematosus if fever and the other clinical features of this disease are absent

Incidence—The disease is still unfamiliar to many clinicians not so much because of its rarity as because the patient is usually under the care of a dermatologist for the rash One of the most remarkable characteristics of the disease is its sex linkage, twenty two out of twenty three cases reported by Baehr Klemperer and Schifrin in 1935 were females eighteen were in the second and third decades of life all but one were between puberty and the menopause the youngest being seven years old the oldest forty five

Etiology—Bacteriologic studies have as yet revealed no clue concerning the cause of this disease Blood cultures are negative unless there is an intercurrent pneumonia or a terminal streptococcus or staphylococcus blood infection In spite of the definite sex linkage no endocrine disease can be identified as a predisposing factor Nor do vitamin deficiencies seem to play even a contributory role As in rheumatic fever and rheumatoid arthritis infection is probably responsible for the disease but its nature has not yet been determined The special predisposition of females would seem to indicate that, whatever the exact nature of this infection or intoxication the disease is conditioned upon a peculiarity in the constitutional reaction of the host It seems to exhibit its effect primarily upon endothelium lined structures capillaries small arteries and veins the endocardium and the synovial and serous membranes

Morbid Anatomy—At the autopsy table the frequent paucity of severe gross anatomic changes and the absence of a distinctive lethal lesion is in striking contrast to the profound toxemia and the train of clinical events leading to the death of the patient It has been shown that the widespread and apparently heterogenous visceral lesions can be reduced to a common denominator Whether the basis of the disease be infection or profound alteration of tissue reactivity it can at least be stated that the con

stant site of the injury lies in the connective tissues of the body

Pericardial involvement occurs frequently and in its severest form appears as a thick, gelatinous, connective tissue completely obliterating the pericardial space This appearance is due to a series of proliferative and degenerative changes of the collagenous tissue underneath the mesothelium Pleuritis is also frequent and presents a picture similar to that of the pericarditis Perisplenitis and perihepatitis are common

The heart may be involved in all of its three layers In about 30 per cent of the cases examined grossly the *endocardium* exhibits a pathognomonic lesion first described by Libman and Sacks The endocardial vegetations may be small and verrucous or large broad and flat They are not limited to the closure lines of the valve cusps but are found elsewhere and on both sides of the leaflets They may extend down the chordae tendineae The mural endocardium of the ventricles is similarly involved A favorable localization is in the pocket between auriculoventricular valves and mural endocardium The lesion is not superficial but begins as a degeneration or necrosis of the subendothelial collagenous tissue of the endocardium The altered tissue becomes by swelling an excrescence on the surface of the endocardium Hence in an additional number of cases early endocardial involvement may be recognized microscopically in the absence of grossly visible lesions The most advanced endocardial lesions are prone to secondary bacterial implantation This when it does occur is either terminal or preterminal

Focal lesions of the interstitial collagenous tissue of the myocardium morphologically identical with those seen in the endocardium and pericardium are present in about 35 per cent of cases Aschoff bodies have not been found

The *kidneys* are generally large and smooth Not infrequently the surfaces show diffuse shallow scarring similar to the atrophy in malignant nephrosclerosis The renal glomeruli often exhibit a distinctive lesion The glomerular loops are thick rigid and deeply eosinophilic Because of their fancied resemblance to loops of bent wire these have been called 'wire loops The glomeruli also show focal necroses of loops These alterations are merely another local expression of the widespread damage to collagen

The small arteries and arterioles of various viscera and especially of the kidneys may show fibrinoid degeneration and necrosis originating in the connective tissue matrix of the vessel wall

An almost constant and characteristic lesion is seen in the *spleen* The central arteries are surrounded by rings of collagenous fibers The accretion of such sclerosing fibrous tissue rings is occasionally extraordinary The spleen itself is not particularly large the average weight being 260 Gm

Involvement of the widely dispersed system of *connective tissues* is exemplified in occasional profound alteration in the retroperitoneal and mediastinal tissues Histologically the changes here are similar to those observed in the pericardium In two cases observed by the author the esophagus was firmly fixed to surrounding structures as the result of this degenerative and productive process in the mediastinal tissues

In those areas of *skin* showing involvement the collagenous tissue of the upper corium exhibits degenerative changes culminating in the most advanced lesions in *fibrinoid degeneration* The smaller blood vessels may also participate The hemorrhages and the epithelial changes are probably secondary to these degenerative changes in the connective tissue

The *lymph nodes* which are enlarged in about one half the cases frequently exhibit focal necrosis Generalized *peritonitis* has followed the breaking down of secondarily infected mesenteric lymph nodes *Bronchopneumonia* is a frequent terminal complication

Symptoms —The salient clinical manifestations are (1) a prolonged irregular fever with a tendency to remissions of variable duration (weeks months or even years) (2) a tendency to recurrent involvement of synovial and serous membranes (polyarthritis pleuritis pericarditis) (3) depression of bone marrow function (leukopenia moderate hypochromic anemia moderate thrombopenia) and (4) in advanced stages clinical evidences of vascular alterations in the skin the kidneys and the other viscera

In the absence of the rash the condition may resemble an infectious polyarthritis The pain and sometimes swelling of various joints may at first make it difficult to distinguish the condition from rheumatic fever or from rheumatoid arthritis Suspicion may first be directed to its true nature by finding a leukopenia the white blood cell count usually ranging between 3500 and 6000 while the polynuclear leukocytes are proportionately reduced The characteristic leukopenia may be replaced by leukocytosis whenever *secondary intercurrent infections* occur such as bronchopneumonia As the disease progresses the hemoglobin falls more rapidly than the red cell count but rarely below 60 per cent In the more advanced stages the blood platelet count is apt to be depressed to about 100 000 occasionally as low as 40 000 Although syphilis is not a factor and the Wassermann test is usually *negative it may at times become positive* or anticomplementary in the later stages of the disease

Suspicion that the illness is not rheumatic fever or rheumatoid arthritis is warranted when red blood cells are found in the microscopic examination of the urine The presence of red blood cells in the urine is due to the development of renal vascular lesions a pathologic *alteration which does not* commonly occur in rheumatic fever without heart failure or in rheumatoid arthritis Small amounts of albumin are also usually to be found The appearance of large amounts of albumin red blood cells and casts resembling the urinary findings of an acute glomerulonephritis signifies the development of extensive vascular changes and of glomerular damage It occurs in the advanced stage of the disease and completely eliminates the diagnosis of rheumatic fever

In addition to arthralgia and arthritis attacks of pleurisy or of pericarditis may occur at any *time during the disease Probably* due to peritoneal serositis some patients may at times complain of abdominal pain and present abdominal distention and diffuse tenderness

When the fever is high and the patient s state is unusually toxic the heart is apt to have a gallop rhythm The electrocardiogram reveals no characteristic changes as a rule except low voltage In some patients a soft systolic murmur is audible at the apex of the heart or to the left of the sternum In most instances it is not to be regarded as evidence of endocarditis as it may be due to the effect of fever or of anemia If it becomes unusually conspicuous it may indicate the peculiar type of endocarditis (Libman Sacks) which develops in the advanced stage of the illness in about 30 per cent of the cases

Either at the onset or else sometimes at a later stage vascular lesions become visible

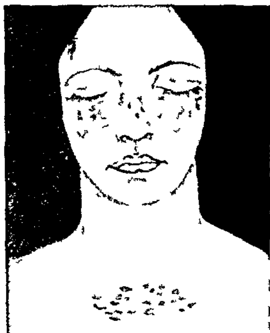


Fig 42—Typical butterfly lesion of lupus erythematosus on the bridge of the nose and the cheeks fading lesions on the exposed portion of the chest

on the skin as erythematous macules or patches which tend to become confluent The rash first appears as a rule upon the more exposed parts of the face the bridge of the nose and the cheeks above the eyebrows on the upper lip the prominence of *the chin and* the edges of the pinna It is also commonly found on the V shaped exposed area of the upper chest It may at times be characteristically located on the ends of the fingers and around the nail beds or as erythematous macules on the thenar and hypothenar eminences the palms occasionally on the ends of the toes and the balls of the feet Areas of skin on parts of the body which are subject to rubbing *or other*

mechanical trauma may become erythematous such as the elbows and knees the shoulders the malleoli the buttocks and the dorsal aspects of the forearms

If the rash has existed for some time minute telangiectases may be scattered in the midst of the erythema as evidence of more permanent vascular changes At times the intensely erythematous areas may present a purplish blush especially on the face fingers elbows and chest due to diffuse extravasations of red cells and plasma Small groups of purpuric or petechial hemorrhages are sometimes seen on the skin and mucous membranes at the height of the disease During periods of remission the erythema tends to disappear but macules of brown pigmentation will then persist in the previously affected areas

Some patients give a history of exposure to the sun immediately before the onset of the disease or of an exacerbation Others who have suffered mildly for weeks or months with a low grade fever and migrating arthralgia expose themselves to sunlight during convalescence and only then develop the facial rash followed by an exacerbation of the illness In other cases no history of exposure to sunlight is given

At the height of the disease erythematous or petechial macules may appear on the mucous membranes especially of the mouth which soon develop into shallow ulcers surrounded by an erythematous or hemorrhagic areola These lesions tend to heal In some patients the tendency to purpura may become marked both in the skin and mucous membranes due to the intense vascular injury and perhaps in part to a tendency to thrombopenia In a few instances hemorrhagic vesicles or even small hemorrhagic necroses develop on the intensely erythematous areas of the face or the hands

Aside from the skin and mucous membrane lesions the progressive injury to the peripheral vascular system results in microscopic hematuria and albuminuria which when marked may give rise to a suspicion of glomerulonephritis Severe examples of renal damage may be associated with fixation of specific gravity of the urine and sometimes in the last weeks of the disease azotemia In spite of severe vascular injury and the renal damage the blood pressure is usually normal sometimes moderately elevated Moderate edema of the face and extremities occurs at times due either to the diffuse vascular disturbance in the skin or to hypoproteinuria If prolonged albuminuria results in profound hypoproteinuria ana



Fig 43—Extensive spread of the rash of lupus erythematosus which at first had a typical butterfly distribution on the bridge of the nose and the cheeks In its advanced stage the rash covers almost the entire face but still does not involve the shaded areas of the face and neck Also characteristic is the V shaped area of erythema on the exposed part of the chest

sarca can develop as a rare terminal phenomenon

Some discrete enlargement of regional lymph nodes is common especially when the skin and mucous membrane manifestations are conspicuous The spleen may be palpable but it is usually not Ophthalmologic examination in advanced cases reveals characteristic evidences of vascular injury perivascular hemorrhages segmentation of arteries scattered fluffy exudates and at times circumpapillary edema and even flame shaped hemorrhages

the favorite remedy of dermatologists There is no reason to believe that it possesses any genuinely favorable influence upon the disease It is to be avoided because it may further depress bone marrow function it may increase the severity of the vascular lesions and it is certainly capable of increasing the severity of renal damage

Remissions in the disease have occurred in patients treated in a variety of ways Confinement to a darkened room or one in which the windows are covered with red cellophane seems to be helpful Although no

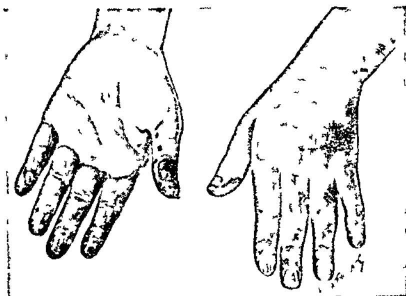


Fig 44—The skin lesions of lupus erythematosus may also occur on the hands and feet When present, the erythema commonly involves the palmar surface of the terminal phalanges and the area of skin around the nail beds on the sides and dorsum of the fingers In the midst of the erythema are petechial hemorrhages and telangiectases The blebs occur only rarely and in cases with the most intense skin lesions Scattered erythematous macules are sometimes observed on the palms on the thenar and hypothenar eminences

Prognosis—The fever and other manifestations of the disease may continue for many months with long alternating periods of exacerbation and of remission In some cases complete remissions may last for years but the ultimate prognosis is grave Occasionally a patient who has been critically ill for months may improve slowly and recover completely However most sufferers from this disease ultimately die Death is due to the toxemia of the disease to renal insufficiency (azotemia) or to an intercurrent pneumococcus streptococcus or staphylococcus infection

Treatment.—No form of specific therapy is available Gold chloride has long been

history of vitamin deficiency can be held responsible for the condition a high calorie diet with the addition of each of the various vitamins has been tried Nicotinic acid has failed to relieve the skin manifestations Most patients have a low blood level and a low excretion rate for cevitamic acid but the prolonged administration of generous amounts of this vitamin to the point of complete saturation does not affect the progress of the disease nor prevent the petechial lesions

Because of the susceptibility of girls and young women to the disease both estrogenic hormones as well as androgens have been employed including large doses of tes

tosterone propionate It is doubtful whether this form of therapy has been beneficial During active febrile periods, the administration of prophylactic doses of sulfadiazine 0 5 to 1 0 Gm twice a day may prevent the secondary infections Sulfanilamide and sulfapyridine in full dosages are indicated for the control of secondary infections with the *Streptococcus haemolyticus* and the pneumococcus They have no influence on the primary disease

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INFECTIOUS MONONUCLEOSIS

(*Glandular Fever Benign Lymphadenosis Monocytic Angina*)

Definition—Infectious mononucleosis is an acute infectious and contagious disease of unknown etiology characterized by fever enlargement of the lymph nodes splenomegaly lymphocytosis and the presence of heterophile antibodies in the blood

History—Under the term Drusenfieber E Pfeiffer in 1889 described a benign epidemic disease in children featured by general malaise fever cervical adenopathy reddened throat without exudate enlarged liver and spleen The glands did not suppurate In 1920 Sprunt and Evans reported a group of benign sporadic cases in young adults characterized by acute onset with fever sore throat enlargement of the lymph nodes splenomegaly and a peculiar blood picture (mononucleosis) Tidy and Morley in 1921 established the identity of these two syndromes Longcope and Downey and McKinlay followed with confirmatory reports Glanzmann in 1930 in a monograph based on a large epidemic in Berne was convinced that monocytic angina was indistinguishable from glandular fever with membranous angina—both clinically and hematologically In 1932 Paul and Bunnell introduced the heterophile antibody test which has been found positive in a high percentage of cases This test which depends upon the presence of sheep cell agglutinins in the patient's serum has been made more specific by *Bailey and Raffel* and by Davidsohn through the use of absorption methods

Incidence—The disease occurs in sporadic and epidemic form most commonly in children and young adults It has been described in North America, South America and in most European countries as well as in Egypt Australia Japan and China In this country the most frequent variety is the sporadic type affecting young persons between the ages of fifteen and thirty Sporadic cases occur in children but are usually mild, and may therefore be over looked Numerous epidemics among children and in boys' schools have been reported but with one exception all of these were prior to the introduction of the serologic test for infectious mononucleosis While infection has been spread by contact from one *adult to another it is doubtful whether the* disease has ever assumed epidemic proportions among adults There were 10 per cent adults in one epidemic It is noteworthy that infectious mononucleosis is frequently recognized in medical students nurses, and hospital personnel where examination of the blood is a routine procedure in diagnosis Numerous cases in the general population are undoubtedly overlooked

Etiology—The causative agent of infectious mononucleosis is unknown The demonstration of the fusospirochetal group of organisms in a considerable percentage of cases with exudative throat lesions has not led to any convincing evidence of their etiologic importance though the pharyngeal exudate injected into guinea pigs has been shown to produce a similar blood picture Isolation of *Listerella monocytogenes* (Nyfeldt) from blood cultures of patients with the disease has been reported but lacks confirmation The most promising field of study that of the filtrable virus has not thus far yielded any conclusive results

Morbid Anatomy—Our knowledge of the pathology of this disease is limited to the study of glands removed at biopsy There is extreme hyperplasia of both lymphocytes

and reticulum at the height of the disease In some of the lymph nodes, collections of small lymphocytes are seen suggestive of early lymphatic leukemia but one does not encounter the complete obliteration of normal structure nor the invasion of the capsule which are found in fully developed cases of leukemia

Symptoms —After an incubation period of about a week and occasionally longer, the disease may begin either insidiously or rather acutely with a varying degree of fever sore throat and enlargement of the lymph nodes and spleen The symptoms occasionally may be so mild as to escape attention entirely or the disease may be rather severe Although the presenting symptoms encountered in some instances are most atypical and unusual (such as jaundice various skin rashes and signs of meningitis) the great majority of cases fall into one of two clinical groups The commonest form encountered in the United States is the *anginose* or *pharyngeal variety* This attacks young adults in a sporadic manner The onset is usually insidious and the initial complaints rather mild and indefinite such as sore throat headache fever sweats general malaise chilly sensations or slight swelling of the cervical glands By the end of a week the lymph nodes of the neck and often of the axilla and groin have definitely enlarged the throat shows a pharyngitis or tonsillitis with patches of exudate suggesting diphtheria but often containing the fusospirochetal group of organisms and the spleen has become palpable in about one half of the cases The liver is enlarged in about 10 per cent of cases The time of appearance of the sore throat and glandular enlargement is quite variable these features may occur early midway or late in the course of the disease For several days the fever may be high 103° to 104° F or even higher and the patient very uncomfortable but there is not the extreme constitutional reaction of severe diphtheria streptococcus infection or acute leukemia The glands do not suppurate Among the uncommon and confusing findings which may mask the actual identity of the disease are jaundice purpura a variety of skin rashes which may resemble measles scarlet fever or typhoid fever and meningismus or true meningitis with 600 or more cells per cubic millimeter mostly lymphocytes in the spinal fluid

The *glandular* or *Pfeiffer type* is most commonly seen in children in sporadic and epidemic forms It is rarely encountered beyond the twentieth year The presenting symptoms are slight sore throat enlargement of the cervical glands and fever In contrast to the anginose form examination of the throat reveals only slight redness but no exudate Axillary inguinal node, and splenic enlargement may or may not be present Involvement of the mediastinal glands may produce cough and enlargement of the retroperitoneal lymph glands may be responsible for abdominal pain nausea and vomiting simulating acute appendicitis Suppuration of the glands does not occur Hemorrhagic nephritis has been described in children as a rare complication After the glands on one side of the neck have markedly diminished in size and the temperature has fallen to normal a recrudescence may occur with rapid involvement of the other side Skin rashes are rare in this type of the disease Recovery usually occurs within a period of two to three weeks

Less frequently the two classical features of sore throat and glandular enlargement may remain in the background or be replaced by other presenting symptoms Thus Tidy emphasizes a febrile form resembling influenza or typhoid Angina is uncommon lymph node enlargement is late in developing and a maculopapular rash appears on the fourth to tenth day In still other instances purpura or a scarlatiniform eruption has been reported Since the introduction of the sheep cell agglutinin test our concept of infectious mononucleosis as a general systemic disease has widened Thus cases which formerly would have been diagnosed as serous meningitis (lymphocytic meningitis) and as catarrhal jaundice have been shown to have a marked increase in sheep cell agglutinins and later have developed glandular enlargement and a typical blood picture

Blood Picture —The red cells hemoglobin and platelets are normal The white blood cells vary in number and character with the stages of the disease During the first few days the total white count may be normal or subnormal with the percentage

of polynuclears normal or slightly increased After six to ten days there is a leukocytosis ranging from 10 000 to 20 000 or above with a decrease in polynuclears and 50 to 85 per cent of the large characteristic cells of the lymphocytic group The predominating cell is a lymphocyte, a varying number of which are abnormal showing deeply basophilic cytoplasm which often contains vacuoles Although there may be difficulty in clas sifying these cells when stained by Wright s method supravital preparations show the majority to be large lymphocytes usually with moderate increase in monocytes By the end of the third week the total white count falls and the percentage of lympho cytes decreases In the glandular form of the disease in children one may encounter an early leukocytosis and polynucleosis which later shifts to a lymphocytosis

Serologic Test —In approximately 90 per cent of cases of infectious mononucleosis the patient s serum contains heterophile antibodies in the form of agglutinins for sheep red blood corpuscles in a titer of 1 to 32 or higher (Paul and Bunnell) Agglu tinins are present in low titer during the first few days but by the second or third week average 1 to 256 or higher falling off sharply as a rule by the fifth week The serum of normal individuals may contain agglutinins in 1 to 8 dilution and patients who have received horse serum may show a titer of 1 to 64 or higher To exclude normal agglu tinins and those due to horse serum injec tions thus making the test more specific for infectious mononucleosis absorption tests with guinea pig kidney and ox cells have been introduced by Bailey and Raffel and by Davidsohn At present there are a cer tain number of seronegative cases in almost every large series reported but further study with the differential absorption test will be necessary before one can definitely state the exact percentage of positive reactions Sero negative cases are believed by some authors to occur more frequently in sporadic cases among children The Wassermann test may be temporarily positive in 6 to 40 per cent the incidence being greater late in the dis ease It tends to return to normal as the heterophile antibody decreases in amount

Prognosis —This is uniformly favorable and the patient is usually well in three to four weeks In some the glands may re main enlarged for several months the lym phocyte percentage or the type of cell may be abnormal and the patient may feel below par for a long time—as long as five or six months

Diagnosis —The diagnosis may be rela tively easy or difficult The sheep cell ag glutinin test and the differential blood count are of the greatest value in differential diag nosis of a disease with such protean mani festations One must remember that infec tious mononucleosis may masquerade under many different guises Its true nature can be recognized by applying the two labora tory procedures above mentioned Confusion may occur with (1) Vincent s angina diph theria or tonsillitis (sore throat), (2) tuber culous adenitis Hodgkin s disease syphilis and mumps (enlarged glands or spleen) (3) influenza typhoid undulant fever scar let fever measles and erythema nodosum or multiforme (fever and skin rash) (4) cat arrhal jaundice acute appendicitis and lym phocytic meningitis (abdominal or menin geal symptoms) and (5) acute lymphatic leukemia granulocytopenia and thrombo cytopenic purpura (blood dyscrasias)

Treatment —Rest in bed is indicated dur ing the febrile period The diet should be that suitable for a mild infection Should the throat lesions show large numbers of Vin cent s organisms a strong oxidizing gargle such as perborate should be used and local applications of 5 per cent neoarsphenamine in glycerin should be made The *sulfonamide drugs* are it appears of value only in case of a complicating hemolytic streptococcus infection Berkley has recently reported complete clinical recoveries within forty eight hours in a small series of cases follow ing the administration of 100 cc of scarlet fever convalescent serum intravenously Further confirmatory studies must be made before final judgment is passed on this type of therapy

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MILK SICKNESS

(*Trembles*)

Milk sickness better known as the trembles is an afebrile disease due to the ingestion of milk milk products or the flesh of animals suffering from the disease

History.—Nicolay and Hay in their "History of Abraham Lincoln" claim that Nancy Hanks the mother of Lincoln died of milk sickness "In the autumn of 1818 the little community of Pigeon Creek was almost exterminated by a frightful pestilence called the milk-sickness " Nancy Hanks was one of the victims

Incidence—At the present time milk sickness is a rare disease but a century ago the condition was common in various parts of the United States It was quite prevalent throughout the Mississippi Valley particularly in Ohio Indiana Illinois and Michigan There is no record of milk sickness having ever occurred outside the United States

Etiology—Although there is some doubt as to the etiology of the disease the evidence seems to be fairly conclusive that milk sickness is caused in the majority of cases by a plant known as white snakeroot *Eupatorium urticaefolium* In New Mexico and Arizona this plant has not been observed but what is apparently the same disease also occurs in these states and is due to another herb the rayless goldenrod *Aplopappus heterophyllus* which probably contains the same toxic agent found in white snakeroot In man the disease results from eating butter or drinking the milk from cattle which have ingested the weed It is also possible for the human being to be poisoned by the beef of cattle that have eaten of this plant When extract of white snakeroot is fed to laboratory animals they become ill refuse food and develop a generalized tremor Couch who was one of the first to isolate a toxin from white snakeroot named it *trematol* which according to Couch exists in the plant partly in ester combination with a resinous acid

Symptoms—Milk sickness is characterized by a gradual onset of weakness loss of appetite and vomiting These early symptoms are followed by constipation and abdominal distress There is no fever but marked thirst is usually noted The mind is clear but in fatal cases coma may precede death by several hours The average duration of the disease is seven to nine days although symptoms may continue much longer

Prognosis—The prognosis is grave in both acute and subacute cases Moseley states that the death rate is about 25 per cent

Treatment—The treatment is purely symptomatic Prophylaxis consists of avoiding meat and milk products of animals with trembles and in pasturing cattle on cleared or plowed land

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MILIARY FEVER

Definition—Miliary fever is an acute infectious disease which occurs in epidemic form and is characterized by abrupt onset of fever excessive sweating prostration and erythematous rash

Incidence—Most of the epidemics have occurred in Europe and the sweating sickness which swept over England during the 15th and 16th centuries was probably miliary fever An epidemic occurred in France in 1907 Zeiss made an epidemiologic study of the disease in Russia in 1932 So far as is

known, the disease has never occurred in the United States

Etiology—The cause of miliary fever is not known nor is its mode of transmission understood The epidemics which have been studied have occurred most frequently in the spring and summer months Individuals of all ages are susceptible The mode of spread is rapid, in this respect resembling that of epidemic influenza

Symptoms—The most striking feature of miliary fever is the profuse perspiration It begins with the onset of fever which continues throughout the course of the disease The eruption which appears on the third or fourth day is usually of the papulovesicular type occurring first on the neck back and chest and later in the axillae and between the thighs Occasionally a purpuric form of the disease with other manifestations of hemorrhage is noted As the rash appears there is gradual diminution in the intensity of the symptoms and after two or three days desquamation occurs Convalescence is characterized by weakness loss of weight and slow recovery

Prognosis—The prognosis is usually favorable but occasionally the patient develops a high fever, dyspnea and rapid pulse followed by delirium and death

Treatment—Treatment is symptomatic

Russell L Cecil

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AINHUM

Definition—Ainhum is a chronic disease of unknown cause usually affecting the little toe and characterized by the formation of a furrow at the digitoplantar fold which deepens and extends until the toe is encircled and eventually separated from the foot

Incidence—Ainhum has been observed chiefly on the west coast of Africa and in Brazil Cases have been reported also from the West Indies and rarely from the southern portion of the United States Apparently white people are not susceptible, all the cases reported have been observed in the black race There is some evidence that ainhum is a familial disease, as it may occur in several members of the same family or in repeated generations of the same family It occurs chiefly in male adults between twenty five and thirty years of age

Etiology—There have been various theories as to etiology Some have claimed that it was related to leprosy This seems however most unlikely, it is much more probable that the disease is a trophoneurosis secondary to some local trauma Castellani believes that the infection is parasitic in origin and that infection takes place through small superficial lesions or wounds often found on the feet of people who do not wear shoes

Morbid Anatomy—In a typical case a fibrous cord replaces the bony structures normally attaching the bone to the foot The skin becomes thickened and the walls of the blood vessels show an endarteritis with a secondary rarefying osteitis

Symptoms—According to Still the little toe is the one affected in 90 per cent of the cases more rarely, the fourth toe and very rarely both the fourth and the little toe are implicated Both little toes may be attacked at the same time, but the condition usually starts in one toe The initial appearance is featured by a crack in the digitoplantar fold of the little toe This extends laterally and finally appears on the dorsum of the toe The distal portion of the toe enlarges and becomes bulbous In the final stages the connection between the foot and the little toe is a slender fibrous cord which permits the toe to wobble in various directions and to interfere greatly with walking

The course of the disease extends over several years if the toe does not undergo spontaneous amputation as a result of injury to the pedicle The disease is practically painless

Treatment—Ainhum is best treated in the early stages by longitudinal incision into the grooved furrow In the later stages amputation is usually necessary

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DISEASES OF ALLERGY

INTRODUCTION

Clinical conditions such as asthma hay fever urticaria, serum disease serum shock, angioneurotic edema eczema and many others involving skin brain (or its membranes) and intestinal tract have gradually come to be recognized and grouped as diseases of allergy The development of a concept in explanation of disease is often as instructive a story as its application Certainly this holds true for the field of allergy today where our knowledge is still vague and far from complete

Although allergy as an explanation of certain human ills dates back only to early years of the present century, the foundations were laid in observations recorded throughout medical literature from its earliest years The physical eccentricity of occasional persons to certain foods was perhaps appreciated by Hippocrates and prompted him to write in his sixty fourth aphorism It is a bad thing to give milk to persons having headache But the major part of the early history consists of records of unusual responses of rare persons to commonly prescribed drugs Such effects having nothing in common with the pharmacologic action were quite properly classified as idiosyncrasies without attempt at explanation or hypothesis

Our present-day knowledge of allergy is really an accidental by product of the general use of diphtheria antitoxic serum which was discovered by von Behring in 1890 Three effects following injection and due to the serum not its antitoxin were soon observed Occasionally it produced a prompt violent reaction (serum shock) that was often fatal Again many persons developed a generalized urticaria in ten to fourteen days (serum disease) and lastly it produced an artificial sensitiveness (anaphylaxis)

This latter result was reported by Theobald Smith in 1904 While working with antitoxin he observed that many of his experimental animals died immediately upon receipt of the second injection when a sufficient interval of time had elapsed after the first one This came to be regarded as essentially identical with the increased sensitiveness to toxins which Richet had reported as anaphylaxis in 1898 hence this term was applied to the Theobald Smith phenomenon Anaphylaxis took the medical world by storm Soon practically every research laboratory gave time to its study on experimental animals Finally out of the mass of conflicting data and theories we emerged with a fairly definite knowledge of the fact of an artificially induced and specific ' sensitization of tissue cells with the serum acting as the reservoir for the excess antibody produced But even today we have no definite knowledge of why certain cells respond with antibody production to parenterally introduced antigens nor of just what antibody is nor of any of the intimate details of the explosive reaction we call anaphylactic shock These problems are receiving attention and their solution will constitute another milestone for biologic science

Naturally anaphylaxis was not long neglected by the clinicians Wolff Eisner suggested it in 1906 as an explanation for hay fever It was known that pollen was the cause—Blackley had proved this in 1873 He recorded the first skin and eye tests using pollens and witnessed local and general reactions not obtainable in persons not suffering from hay fever In 1909 Gillette collected the scattered records of cases of sudden death following diphtheria antitoxin injections This too was regarded as anaphylaxis He first called attention to the similarity of symptoms to those of asthma but noted the important fact that serum shock had in most cases followed the first injection Thus asthma was brought into the field as well as urticaria which was a common accompaniment of the dyspnea and was also the chief symptom of serum disease It then seemed simple Hay fever asthma and urticaria were the human manifestations of anaphylaxis That this is not strictly so

will be evident from later discussion but this was the starting point for the development of the hypothesis of sensitization as the explanation for the group which we now call diseases of allergy

This word meaning altered reactivity was coined by von Pirquet in 1906 to indicate certain changes of reaction induced by first injections and not related at all to immunity conferred This opinion was voiced by von Pirquet not only as a result of his own observations on altered reactions to a second and subsequent injection of smallpox vaccine and horse serum, but also to the already recorded findings of similar changes caused by other antigens noted by Richet von Behring Wolff Eisner and others Today largely because it is conveniently short and euphonious allergy has been adopted by common consent to denote the sensitization reaction of man hence it either includes or is synonymous with hypersensitiveness sensitization idiosyncrasy anaphylaxis and atopy

The grouping under allergy of such an array of seemingly unrelated and dissimilar conditions as hay fever urticaria asthma eczema finds a basis in *clinical association* and *immunologic relationship* (1) The *clinical association* was well demonstrated in a study of 621 cases of asthma and hay fever by Cooke and Vander Veer in 1916 They showed that a large percentage of the cases had past or present histories of urticaria eczema angioneurotic edema and various other curious and unusual food and drug reactions and they further established that these same conditions were common among antecedents collaterals and descendants In other words allergies were manifestations of a familial trait (2) The *immunologic relationship* rests upon the concept of sensitization to explain all the unusual and abnormal reactions of cells to the presence of substances which under usual conditions in normal persons produce no obvious reaction whatsoever

We may define the allergic state as one of potential specific reactivity due to the existence in certain cells of a mechanism (antibody) which mediates the linkage of the cell to the specific substances (antigen)

Allergy is the resulting reaction qualitatively altered from the normal of the species when union of antigen with sensitized cell is effected This broad definition regards as allergy all specifically mediated reactions hence criticism may be made as it would include the reactions resulting from the transfusion of an incompatible human blood in man It is true that the word 'allergy is not yet used for this purpose but because this special antibody is normal physiologic spontaneous and hereditary is certainly no argument as we shall see against the inclusion of such lytic and agglutinative reactions as allergies

It must be understood that allergy is not a single or uniform biologic phenomenon There are different pathogenic etiologic pathologic and immunologic as well as clinical varieties We shall consider these in order

Pathogenesis —*Induced Physiologic or Normal Allergy* —1 Injection of small amounts of horse serum as diphtheria antitoxin produced serum sickness in about 10 per cent of all cases With the use of large doses of pneumococcus antiserum the incidence rose to 90 per cent That individuals after serum disease remain allergic for some time can be proved by the positive skin reaction to a test dose of serum and by the serum changes later discussed

2 A dermatitis often results from contact with certain dyes and vegetable oils Studies with the oils of ivy and primula have been most illuminating Without details we may sum up by saying that newborn babes and adult Esquimaux do not develop dermatitis with the first application of these oils Following Low s studies with primula Straus found that the second application of ivy oil to the infant s skin two to four weeks after the first gave an eruption in 73 per cent of those retested Obviously the skin eruption is not due to any toxic or irritative quality of the oil but is explained as a sensitization developed as a result of an earlier contact

3 Not infrequently infection with a particular type of bacterium produces a state of reactivity to that organism or its products A reaction to tuberculin is well recognized to exist in practically all cases infected with the tubercle bacillus There is no reaction to the test in the uninfected

Here are three typical examples of clinically different reactions which are explained

by allergy since the primary action of the antigen is neither toxic nor irritative One sensitization results from contact with serum another from ivy oil and the third follows tuberculous infection Since they are or may be specifically induced at will by proper contact and since the great majority of the species react alike in each instance I have grouped them under the general head ing of Induced Physiologic or Normal Allergy

Spontaneous Pathologic or Hereditary Allergy—The important group of clinical allergies—asthma hay fever eczema angio neurotic edema etc—forms a striking con trast to the induced allergies They occur in but a small proportion something under 10 per cent of the population they have never yet been artificially produced by any sort of contact they seem to appear spon taneously and paternal as well as maternal heredity has been proved to be an impor tant predisposing factor The cause of the development of sensitization is not so read ily explained in these diseases Studies have shown that skin sensitizing antibodies can not be transmitted through the placenta to produce passive sensitization of the fetus One school believes today that they are analogous to experimental anaphylaxis that is induced by contact stimulation A point in favor of this idea is that allergies in infants are frequently due to foods The sensitization to substances not included in an infant s diet may be assumed to be the result of contact during intrauterine life Then too there are certain serologic simi larities to be discussed later

But this concept does not explain the many vagaries of the sensitization of man It does not take account of the part that heredity has been shown to play nor of the fact that many of the antigenic (reacting) substances are nonprotein nor of the fact that the commonest allergens are substances with which there is relatively little contact On the other hand to prove the entire ab sence of contact prior to the sensitization is impossible

Following the thought suggested by Burky s work with staphylococcus toxin and in line with Bailey s findings of hemol ysin in serum of rabbits infected with Bacil lus lepisepticus together with the clinical observation that many allergies follow in the wake of acute infections it may be that bac terial products or toxins act synergistically to enhance the antigenic property of a sub stance that happens to be at hand at just the proper moment It may even be that the real antigen is not the particular substance as we know it egg albumin or pollen protein or quinine but is rather some derivative of these substances with a special molecular configuration After all allergic reactions are fundamentally chemical or physiochemical rather than biologic hence the mechanism may be initiated by one molecular structure with a resulting sensitization to chemically related structures occurring in biologically unrelated fields

But there still is the possibility that this type of allergy is spontaneous The thesis has not been disproved and support for it is found in the lysins and agglutinins which normally appear in the various blood groups They are determined solely by heredity and not by contact stimulation However it must be admitted that we do not yet know how the sensitization starts what deter mines the allergen or the clinical form of the allergy for the particular case From among our many contacts why one becomes reac tive to pollen another to food while a third develops allergic symptoms from infection is not explained by the mere assumption of contact and general hereditary susceptibil ity This type of allergy is further distin guished by the extreme degree of reactivity by the multiplicity and variety of the sen sitizations and their long continuation even in the complete absence of contact At pres ent we must say that contact may or may not be necessary to set off the allergic mech anism in man If it is then a very mild one only may be needed to initiate a variable highly reactive and self perpetuating allergy to one or more substances that seem to be predetermined by nature or heredity as other contacts great and small are ineffec tive

Etiology.—The exciting causes of an allergic reaction in man that is the antigens are many and varied They may be absorbed by ingestion inhalation injection from a focus of infection or from external contacts The list contains the pollens danders and many other air borne substances of animal

and vegetable origin foods drugs, therapeutic sera and bacteria and their products Sensitization is not limited to proteins though they are the commonest antigens, but it is known to exist to fats, oils, resins, metals, and to such simple organic compounds as the alkaloids and benzol ring derivatives

Pathology —It is obvious from what has been said that allergic reactions show several different types of cellular reactions thus exhibiting a varying functional or organic lesion

The simplest pathology is the functional *edema* and *hyperemia* occurring singly but as a rule together This lesion is illustrated in the urticarial wheal and in vasomotor rhinitis

The inflammatory organic lesions of allergy may be *exudative* as in eczema and related dermatoses *productive* as in hyperplastic rhinitis and sinusitis and periarteritis nodosa In some cases *necrosis* and *ulceration* occur as in certain drug allergies lupus erythematosus and others

Hemorrhagic lesions also occur The purpuras of the nonthrombocytopenic and symptomatic groups are allergic

In general the histology varies depending upon the tissue involved the type of allergy and the nature of the antigen A detailed discussion is not required We only wish to indicate the varied histologic picture

Immunology —(1) Experimental anaphylaxis (2) serum disease in man and (3) asthma from contact with horses or on administration of horse serum are regarded by some immunologists as identical because of certain identical features and by others as essentially different because of important differences

(1) In the animal foreign protein injections produce cellular and serologic changes which are spoken of as anaphylactic Reinjection of the protein at the proper time produces shock and death immediately The sensitization can be transferred to another animal by the serum The serum demonstrably contains three immunologic antibodies (*a*) precipitins shown by suitable test (*b*) muscle sensitizing bodies shown by the response of the uterine strip (Dale reaction), and (*c*) skin sensitizing bodies first demonstrated by Cooke and Spain Using the Prausnitz Kustner technic a small amount of the sensitive serum was put into the superficial layer of skin of a normal man When later tested with the specific serum this site gave an immediate urticarial wheal whereas other portions of skin did not react This serum transfer of skin sensitiveness from sensitized animal to man is not so regular a finding as is the precipitin or the Dale reaction but it is definite and has been confirmed by de Besche and others

(2) In man injected with sufficient serum sensitization develops in roughly ten days at which time a generalized urticarial eruption appears (serum disease) In this serum are found the same three antibodies as in the animal—the man has been artificially sensitized and remains so for some time thereafter In other words, serum disease is but an incident in the development of the sensitization He is then anaphylactic as is the animal but not asthmatically allergic to horse contact It is probable he would die in shock if injected at the proper time There are of course no definite experiments but clinical reports sustain the idea This artificially sensitized man loses his reactivity in time measured by weeks

(3) The human being who has developed asthma and reacts on skin test with the serum frequently has no history of contact with horses or often a very slight one He is the person who reacts violently immediately often fatally if injected with serum Serologic studies in these cases have shown neither precipitins nor smooth muscle sensitizing bodies but the serum does contain the transferable skin sensitizing antibodies These patients never purposely sensitized develop a degree of allergy infinitely greater than that ever produced artificially by large amounts of injected serum and they possess a sensitization that once begun usually lasts a lifetime even without specific contact The literature does not appear to contain any reports of attempts to desensitize the artificially sensitized nonasthmatic man Theoretically it should be possible It has been attempted but not successfully with the naturally sensitized asthmatic

The only point of identity then between the man who has been artificially sensitized and the so called spontaneously sensitized

asthmatic is that both are specifically reactive by the skin test, giving an immediate urticarial wheal and the sera of both transfer this reactivity to normal human skin It is upon this slender evidence that identity is claimed for the induced physiologic anaphylaxis and spontaneous or hereditary asthma

There is no knowledge of the immunology of induced allergies represented by the tuberculin reaction and dermatitis venenata In the absence of any serum antibody demonstrable by the passive transfer test we assume the existence of a cellular antibody to mediate the abnormal response to substances which are not in themselves reactive

Immunologic Types of Clinical Allergies —In spontaneous or hereditary allergy clinical observation indicates two immunologic types that may be differentiated depending upon whether the symptomatic reaction occurs *immediately* (within an hour) upon contact or whether it is *delayed* Let us see what important differences are found

(*A*) The Immediate Type —A patient states that contact with horses will give asthma and hay fever within a very few minutes When tested with the dander extract in the skin an immediate wheal with itch and erythema develops in a few minutes A drop of the extract in the eye produces erythema itching and tearing just as quickly If the extracts of dander dust pollen or food give an immediate skin test reaction then clinical contact with that substance will in general produce the prompt clinical reaction A clinical story then of a general or systemic reaction following immediately (one hour) upon a contact whether inhaled or ingested will in general be substantiated by an immediately positive skin test with that substance In the serum of these patients the presence of the skin sensitizing antibodies is demonstrable by passive transfer to normal skin The scratch or intradermal skin tests are valuable in diagnosis in this immunologic group and in this group alone This is the general rule There are exceptions

(1) Positive skin tests do not always signify clinical sensitiveness This is illustrated by a patient found positive to skin test and negative to eye test with ragweed extract with no clinical history of hay fever Immediately after a small injection of ragweed extract the patient gave a general reaction with urticaria cough sneezing and watery eyes The test indicated his allergic state but he did not have clinical hay fever (2) Negative skin tests do not always mean absence of immediate clinical reaction As a rule the so called ' nonantigenic substances like aspirin and quinine etc do not give positive skin tests when they produce an immediate general reaction of asthma without urticaria My records show only one case of an immediate aspirin reaction with asthma and urticaria and here the skin test was positive Also in my records there is but one case giving an immediate asthmatic test reaction without urticaria to fish protein and here again the skin test was itself negative The subject was similarly sensitive to aspirin Such cases are great rarities

(*B*) The Delayed Type —A clinical allergic reaction perhaps an urticaria or an edema or even an asthma may begin not immediately, but anywhere from several hours to several days after contact with a particular substance In such instances not only does the reaction always occur but it occurs after essentially the same incubation period Frequent recurrences of the reaction do not serve materially to shorten or lengthen that time interval although the severity of symptoms may increase In such cases the skin test with the substance proved by clinical test to be the cause is uniformly negative even when the clinical reaction is urticaria The passive transfer test is also negative Obviously we are dealing with a mechanism of reaction which is immunologically different from the *immediate* type This we call *delayed* allergy Its mechanism is unknown while the fact of its existence is clear It resembles serum disease only in its incubation period and perhaps in the rash It differs however in having none of the serologic findings and no positive skin test at any time In this group we see reactions to foods drugs and bacterial substances but very rarely to air borne substances Many of the cases of urticaria and angioneurotic edema both external (cutaneous) and internal (abdominal and cerebral) of eczema and other dermatoses belong in this group also all allergies of infective origin producing

bronchial (asthma), nasal and skin symptoms

Certain lesions of infectious disease are today attributed to allergy as for example the rash of scarlet fever the joint manifestations of certain arthritides and the inflammatory and necrotic lesions of tuberculosis to mention but a few Some of them belong in the group of physiologically induced allergies as they are the usual and normal response of mankind but others belong in the pathologic group in which like asthma hereditary influences are important Whether or not the mechanism of the allergy in the two groups is identical is not known today

Clinical Types—There seems to be no part of the body—no organ no tissue cell—that may not be sensitized and respond with one or another of the several pathologic or immunologic types of reaction we have discussed but the tissues derived from the ectoderm, skin, mucous membrane, and nervous system are most commonly involved Hence we have in the skin such allergic lesions as urticaria purpura eczema contact dermatitis, lupus erythematosus dermatitis herpetiformis and others In the nose vasomotor and hyperplastic rhinitis and sinusitis are the usual manifestations In the abdomen an allergy may be manifested by simple indigestion acute and chronic gastro enteritis and colitis or it may simulate an acute condition within the abdomen requiring surgery Cerebral allergies are also recognized giving rise to migrainous and epileptiform attacks paralysis and coma as well as symptoms of multiple sclerosis and encephalitis

Diagnosis—A history of allergy in direct or collateral antecedents or in the sibs or descendants or a well defined allergy such as hay fever in the personal history makes for a presumptive diagnosis of allergy in a patient with obscure long standing persistent or recurring symptoms Especially is this true when such symptoms are referable to lesions in tissue of ectodermal origin

The skin test for allergy should seek to reproduce the histologic picture of the clinical allergy under study for example one cannot and should not expect to make a diagnosis of the cause of eczema which is an exudative and delayed allergy by means of the intradermal test which can only indicate the edematous immediate type of reaction Disregard for this fundamental principle has led to great confusion and error

The skin tests are important diagnostic aids but only when properly interpreted and only in that immunologic type of allergy we have described as 'immediate' Other special diagnostic measures of value are the environmental tests and restrictive diets which will not be discussed in detail here

Prognosis—Most of the important clinical allergies are of the type we have described as spontaneous or hereditary Thus they represent an ingrained constitutional defect Such individuals are likely to have not only recurrences but different clinical varieties of allergy reappearing at any time through life It should be appreciated that while we may control the evidence of allergy by avoidance of the exciting agent or injection against it we do not cure the sensitization nor prevent its reappearance in some other form to some other allergen

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HAY FEVER

(Allergic Coryza Vasomotor Rhinitis)

Introduction—Nasal allergy or allergic coryza manifests itself in different clinical types according to the nature of the substance producing the reaction The immunologic mechanism of the vasomotor reaction

is that of the immediate type of allergy in which positive skin test and passive transfer reactions are obtained When the clinical reaction is due to pollens it is termed seasonal coryza' When a similar condition exists continually or intermittently throughout the year depending entirely upon contact with the allergen it is called perennial coryza

ROBERT A COOKE

SEASONAL HAY FEVER

(*Rose Cold Pollinosis*)

History —The following facts stand out as important in the development of our present conception of the nature the causative factors and the treatment of hay fever Bostock in 1819 identified the seasonal coryza as a clinical entity Elliotson in 1831 suggested the pollens as causative factors In 1873 Blakeley a hay fever victim used extracts of pollens upon himself and was able to precipitate an attack Dunbar conceiving that the pollen contained a toxic albumin attempted to immunize horses against the toxin He believed that the serum of injected horses contained a specific antitoxin and this immune horse serum was used in treatment and sold under the trade name of Pollantin This serum not now in use, was never shown to contain a specific pollen antibody Wolff Eisner in 1906 suggested that hay fever was a specific anaphylactic reaction Freeman and Noon in 1911 were the first to publish results on the treatment of hay fever by active immunization with pollen extracts Clowes in 1913 reported on the specific reactions exhibited by hay fever cases Cooke in 1915 reported on 144 cases treated by injection with extracts of pollen Since this time a considerable amount of work has been done the important pollens have been determined and the technic of diagnosis and the method of treatment have been fairly well systematized

Etiology —The air borne pollens are the important etiologic factors but almost any pollen may cause hay fever when it is presented in sufficient concentration For the eastern part of the United States it is possible to distinguish 3 seasonal varieties of hay fever The *spring type* begins at the end of March or early April and extends to the end of May This is due to the pollens of trees especially the oak elm birch hickory ash and poplar The *summer type* beginning at the end of May and extending to the middle of July is caused by the pollens of grasses plantain and sorrel The *fall type* begins in the middle of August and continues until frost The pollens of the ragweeds are mainly responsible for this type In the southwestern states the amaranths artemisias and mountain cedar are also factors For detailed information monographs must be consulted In 1928 Parlato showed that the dust of the caddis fly also caused typical hay fever

As a predisposing factor in pathogenesis heredity is important

Incidence —Accurate statistics are not available Hay fever usually begins between the tenth and thirtieth years Both sexes are equally liable

Morbid Physiology —In 1919 Ramirez reported what appeared to be a passive transfer of hypersensitiveness by means of blood transfusion The donor had clinical symptoms of coryza and asthma on exposure to horses Following transfusion the recipient developed an attack of asthma after exposure to a horse He had never had asthma before In 1921 Prausnitz and Küstner demonstrated that the serum of a fish sensitive patient when injected intradermally into a normal man produced a localized skin sensitiveness The injected site reacted to the fish preparation whereas the other areas of skin in the normal man showed no response This phenomenon known as passive transfer of sensitiveness was confirmed by de Besche It is now generally accepted that the blood serum of certain clinically sensitive cases contains antibody which specifically sensitizes skin cells to the allergen to which the donor is sensitive This is the type of allergy met with in most of the seasonal and perennial hay fever cases

The earliest observations on cases of human allergy have shown that the immediate reaction can be demonstrated in the skin as well as in the mucous membranes of individuals with clinical hay fever and asthma This general skin sensitiveness is made use of in diagnosis The functional change in nasal membranes in hay fever is purely vasomotor

Morbid Anatomy —There is no organic pathology in uncomplicated seasonal coryza The bony and cartilaginous structure and the mucous membrane of the nose may be as normal in appearance in patients with hay fever during the free period as they are in the normal man Organic lesions such as suppurative sinusitis polyposis and hyperplastic rhinitis and sinusitis are the result of infection of the nasal membranes and are not uncommon

Symptoms.—The symptoms of hay fever are essentially local and due to the reaction at the point of contact in the mucous membranes of the eye, nose and pharynx They vary considerably in severity In occasional cases peculiar variations have been noted such as those in which the symptoms are entirely nasal and there is no clinical ophthalmic reaction Or more rarely one eye only is involved or one eye is much more sensitive than the other During the attack the symptoms vary greatly in severity from day to day or from hour to hour They consist of an *itching* and *congestion* sometimes even of an edema of the mucous membrane of the sclera and conjunctiva *Photophobia* of greater or less degree results There is itching of the nose and sometimes of the skin over the nose and the face *Sneezing* occurs in paroxysms is violent and is accompanied by a thin alkaline, irritating mucous discharge Congestion and edema of the mucous membrane of the nose occur and when the edema is great there may be complete obstruction to nasal breathing Itching is often felt in the ears on the roof of the mouth and in the pharynx

The clinical picture of seasonal hay fever is quite typical It is particularly characterized by its strictly seasonal occurrence and by the fact that in any given patient the attack from year to year begins and ends on approximately the same date This is quite readily explained by the fact that in any given locality the pollination of plants is very little influenced by weather variations

Complications.—*Multiple Reactions*.—Over 50 per cent of hay fever patients are hypersensitive to more than one allergen Approximately 33 per cent of those with the summer type of hay fever are clinically sensitive also to the pollen of ragweed and it is not uncommon for seasonal hay fever to begin in the spring and continue until frost The essential point is that attacks do not occur during the winter months Seasonal hay fever is not infrequently combined with the perennial type In this case there is a perennial disturbance, with exacerbations occurring in the pollen season These complex manifestations can be recognized only by means of the diagnostic tests Occasionally typical seasonal hay fever the fall type for example does not cease at the time of frost but continues into the winter This may be the result of an additional reaction or a secondary sinus infection

Infection.—Infections of the paranasal sinuses occur in a large percentage of cases but in only a *relatively small* percentage does this infection become clinically important and warrant *special treatment*

Asthma.—Asthma may be caused by the *allergic reaction to the* pollen In such cases it begins one or two weeks after the onset of hay fever but *terminates with it* This type occurs in about 30 per cent of all cases of hay fever There is also a type of asthma which results from infection of the paranasal sinuses This form usually develops late in the course of hay fever and may persist long after the seasonal limits of hay fever

Diagnosis.—We shall limit discussion to the diagnosis of causative factors An important index of probable causes of hay fever is obtained by an accurate history of the time of onset and offset of the attack One should also bear in mind that multiple sensitizations are present in about half of the cases so it is wise to test also with the more important substances that are factors in perennial hay fever (See Nonseasonal Hay Fever) If a reaction is obtained to one of the grasses the reactions to pollens of all other grasses will be about the same degree We believe these pollens are biologically identical If a patient reacts to one of the varieties of ragweed a similar reaction is always obtained with the others The same cannot be said however for the pollens of trees No uniformity of reaction has been found here except with species of the same genus For this reason all of the more important tree pollens must be tested if the patient s history indicates sensitiveness to this group

The diagnosis of the specific pollens to which a person may be sensitive is made by means of cutaneous and ophthalmic tests

Cutaneous Test.—The cutaneous test may be performed in two ways In the *scarification method* the desiccated or fluid extract of pollen or the pollen itself is applied to a small scarified area of the skin In the *intradermal method* the extract of pollen is introduced into the most superficial layer of the skin through a fine hypodermic needle

(26 gauge) The amount injected in any one test is about $\frac{1}{50}$ to $\frac{1}{100}$ cc This forms a small papule from 2 to 3 mm in diameter Using either method, from 6 to 8 tests may be made at one time The intradermal *method is the more delicate* and accurate of the two but in inexperienced hands the *scarification method is perhaps safer*

Tests are negative when there is no increase in the size of the original papule no zone of hyperemia and no itching Positive reactions are designated as "marked," moderate' or 'slight In the *marked reaction* from five to fifteen minutes after the introduction of the extract there develops an urticarial wheal with irregular outline and pseudopod projections extending out into a zone of hyperemia This wheal may become several inches in diameter if the reaction is very marked When the wheal exceeds 1 inch in diameter the subject is exquisitely sensitive to the extract in the concentration used and a general or constitutional reaction may result Itching practically always accompanies these reactions The wheal usually fades within two to four hours and becomes blended with the surrounding zone of hyperemia which may last from six to twenty four hours Occasionally even at the end of thirty six hours there is still hyperemia and edema at the site of the test *Moderately positive* reactions are merely less severe than the marked reactions There is a decided increase in the size of the papule without the marginal irregularity or pseudopod formation characteristic of the marked reaction There is a zone of hyperemia and itching Such reactions usually fade within two to four hours A *slight reaction* is indicated by very little increase in the size of the original papule There is a small zone of hyperemia and itching may or may not be present Such manifestations fade in one to two hours

Absolute reliance cannot be placed upon the positive skin test in diagnosis A positive reaction that can be verified at will is pathognomonic only of cutaneous allergy it does not always connote clinical allergy

Ophthalmic Test—A drop of the pollen extract used for the skin test is instilled into the conjunctival sac When the *test is negative* there is no change A *positive reaction* is indicated by itching of the eye lacrimation and congestion of the scleral and conjunctival mucous membranes In some cases the pollen extract is carried through the nasal duct and causes a nasal reaction with sneezing itching and serous discharge A positive ophthalmic test is practically pathognomonic of clinical sensitiveness and indicates that whenever the patient comes sufficiently in contact with this allergen under natural conditions a mucous membrane reaction is bound to ensue The ophthalmic test suffers from the fact that only a limited number of tests can be made and that it cannot be employed during an attack

As to the relative value of the cutaneous and ophthalmic tests we may say that they are to be regarded as complementary Practically one depends upon the skin test for reactions which in case of doubt may be verified by the eye test The cutaneous test indicates more accurately the degree of somatic reactivity and is used for the titration of sensitiveness which is so essential to proper therapy

Pollen Preparations—Of the many methods of preparing pollen extracts the most satisfactory is that in which the extract used for the therapeutic injections is identical with the one used for the cutaneous and ophthalmic tests The pollen allergens have been shown to be protein therefore the most satisfactory method of standardization of pollen extracts is by their protein nitrogen content. Protein nitrogen 0 000001 mg has been designated as one pollen unit using the technique of Cooke and Stull No method of standardization is entirely accurate for biological activity lessens in aging solutions out of proportion to determinable chemical change As this deterioration is due partly at least to enzymatic activity care must be exercised in keeping the extracts cold during preparation and throughout the period of use Of course care in the collection and storage of pollen for future use is equally important When proper attention is paid to these details the extracts are entirely satisfactory for about one year

Recent work has shown that there are at least three different proteins in ragweed pollen fraction #1 so-called has the chemical properties of a plant albumin fraction #2 resembles a plant proteose and fraction #3 which is alkali soluble has the qualities of a plant glutelin Ragweed sensitive patients do not all react alike to these fractions One patient may be more sensitive to one fraction and the next to another fraction Fraction 1 appears to be more active and important and is highly antigenic Fraction 2 seems to be largely responsible for the constitutional reactions in those patients that take pollen injections with difficulty as this *fraction is a poor antigen yet highly reactive in certain persons*

Titration of Sensitivity—It is necessary to determine not only the reacting pollens but also the patient's degree of sensitiveness which varies markedly This is important for the more sensitive cases cannot take the therapeutic doses required for the less sensitive This

titration of sensitivity is carried out by means of the usual test solutions of different strengths

Three test solutions containing 10 100 and 1000 units per cubic centimeter respectively are convenient for this purpose The *very sensitive* cases (*A*) give marked skin reaction to a test dose of 10 units per cubic centimeter and a marked plus wheal (2.5 cm in diameter) to the solution of 100 units per cubic centimeter *Moderately sensitive* cases (*B*) give marked reaction with 100 units per cubic centimeter and a marked plus *reaction with 1000 units per cubic centimeter* *Relatively insensitive* cases (*C*) give marked reaction with 1000 units per cubic centimeter

This grouping of cases must be regarded as only approximate but it has a very definite practical value in dosage

Treatment —*Climatic* —There is no particular locality in which the patient suffering from the *spring* or *summer type* of hay fever may be assured of complete relief except upon the ocean Patients suffering with the *autumnal type* may avoid the attack in the White Mountains on the coast of Maine, in California and Europe As a matter of fact pollen free air is all that is required for comfort This may be accomplished by air conditioning a room by simple filtration or dehydration Many practical machines are now on the market

Drug Therapy —Cocaine of course temporarily modifies the attack but except in case of the utmost severity its use is not warranted Epinephrine and ephedrine in the form of nasal sprays may help but are often irritative and produce a secondary reaction that is worse than the original condition Atropine sulfate ($\frac{1}{100}$–$\frac{1}{150}$ grain) lessens the discharge but does not relieve other symptoms

Other measures such as zinc ionization of the turbinates or the application of phenol have been used in an attempt to prevent the attack or as a method of cure during the attack Experience has now shown that these are not successful and may be dangerous Asthma which has never existed before has followed the use of these measures for the seasonal as well as the perennial type of disturbance

Specific Treatment —It has recently been shown that injections of pollen extracts in specifically sensitive hay fever patients induce definite serologic changes These are demonstrated by the newer methods of quantitative serum titration using nonsensitive test subjects for passive transfer The protection obtained by specific treatment does not appear to depend on desensitization for the amount of serum antibody remains the same or may even be increased The protective mechanism afforded by specific injections is not yet completely understood

Prophylactic Treatment —The specific treatment of hay fever by means of pollen extracts is well established Having first determined by means of the tests the proper pollen extracts to be used and the degree of sensitiveness of the patient to these pollens as outlined under Diagnosis treatment is begun with subcutaneous injections about ten weeks in advance of the expected attack Increasing doses are given at approximately weekly intervals according to the Table of Suggested Dosage

The maximum dose which is attained at or about the period of clinical onset is given weekly without further increase throughout the season With the earlier doses there is usually some reaction at the site of injection with swelling and itching lasting fo twelve to twenty four hours If the local reaction persists longer than forty eight hours the subsequent dose should not be increased for fear of a general reaction

Phylactic Treatment —Phylactic treatment is necessary when patients apply for treatment during or just before the onset of the attack Here the same method of diagnosis by means of the cutaneous test is necessary The ophthalmic test is useless after the attack has begun The injections are carried out according to the Table of Suggested Dosage and maximal doses are continued every three days to the end of the season

Perennial Treatment —With the idea that long continued injections lead to better results and may eventuate in a permanent *cure* patients prophylactically treated to a maximal dose are continued under treatment with a maximal injection every three to four weeks throughout the year Such monthly injections must be given for several years This type of therapy is not applicable to all cases

Constitutional Reactions —These begin very quickly after the injection sometimes within a few minutes practically always within an hour The sooner they begin the more severe and the more dangerous they are The symptoms of these reactions

are first itching of the palms of the hands then rapidly developing general erythema and urticaria with marked coryzal symptoms and asthma Occasionally there is edema of the eyelids and of the face Asthma is the symptom that makes any reaction dangerous and an asthmatic attack may result even if there is no clinical history of asthma with the hay fever itself These constitutional reactions should be immediately recognized and a tourniquet applied very tightly above the site of injection in order *to delay further absorption into the general* circulation The patient is then treated by a liberal subcutaneous injection of epinephrine (1 1000 solution in amounts of 0.5–1 cc) This should be repeated frequently in order to control the attack If the attack is very severe the injection should be given intravenously No limit should be put upon the dosage for under these conditions enormous quantities are tolerated *Morphine* is also indicated in the usual dose In very severe attacks when there is indication of dilatation of the heart caused by the intense dyspnea *strophanthin* administered intravenously is helpful

RESULTS OF TREATMENT —The reason for the beneficial results from injection of pollen extracts has not yet been discovered It is not desensitization, for after a complete course of treatments the cutaneous and ophthalmic reactions are still obtained with about the same degree of intensity as before the treatment The effects of seasonal injections are not permanent The course of treatment must be continued from year to year although in general it is observed that the sensitivity tends to decrease after several years of treatment That the treatment is effective is demonstrated by the clinical results that have been obtained consistently *over a long period of years In 80 to 90 per* cent of the patients treated the coryzal symptoms are almost entirely eliminated but it is very difficult to secure their complete absence throughout the entire season In those patients in which asthma occurs as a part of the reaction the results are even more satisfactory In over 50 per cent of the patients with clinical asthma this symptom is entirely controlled The results of phylactic treatment are sufficiently good to warrant its use but they are not as good as those of prophylactic injections The results of perennial treatment are better than the seasonal but it is too soon to evaluate the chances of permanent cure by this method

SUGGESTED DOSAGE ACCORDING TO DEGREE OF SENSITIVITY

PROPHYLACTIC[1]			PHYLACTIC			
A[2] UNITS	B[3] UNITS	C[4] UNITS		A[2] UNITS	B[3] UNITS	C[4] UNITS
5	10	50	1st day	1	10	50
10	20	150	2nd day	1	10	50
15	40	300	3rd day	1	10	50
25	70	500	After 2 days	2	20	100
3	100	750	2 days	3	30	200
50	200	1 000	3 days	4	40	300
75	400	1 500	3 days	6	60	500
125	700	2 500	3 days	8	80	700
175	1000	4 000	3 days	10[6]	100[6]	1000[6]
250	1500	6 000				
300	2000	8 000				
400	3000	10 000				
600	4000	12 000				
800[5]	5000[5]	14 000[5]				

[1] Prophylactic doses given weekly
[2] A Very sensitive cases
[3] B Moderately sensitive cases
[4] C Relatively insensitive cases
[5] This dose is continued weekly to end of season
[6] This dose is given every three days to end of season

ROBERT A COOKE

NONSEASONAL HAY FEVER

(*Perennial Hay Fever Vasomotor Rhinitis*)

Definition —This clinical condition differs from the seasonal type in its specific cause and in the fact that the attacks are not regularly seasonal, but may be continuous or paroxysmal throughout the year The pathogenesis functional pathology, symptoms complications diagnosis and diagnostic technic are the same as in the seasonal hay fever

Etiology —The most important excitants are

1 *Absorbed by inhalation*
   (*a*) Animal danders horse cat dog rabbit goat, cow, guinea pig chicken goose duck
   (*b*) Vegetable powders orris rice corn wheat seed of cotton kapok, flax castor bean dust of hay and straw (not pollen) hops
   (*c*) House dust
   (*d*) Spores of various fungi
2 *Absorbed by ingestion*
   (*a*) Foods milk egg wheat fish shellfish nuts chocolate coffee buckwheat celery bean white potato banana
   (*b*) Drugs quinine aspirin ipecac senna iodine morphine phenol phthalein
3 *Absorbed from focus of infection* Para nasal sinuses

When symptoms are caused by the ingestion of the allergen the coryzal symptoms are usually but the minor part of a general reaction with urticaria erythema angio neurotic edema asthma and gastro intestinal disturbance

Air borne substances absorbed by inhalation are the actual causes in most instances They are encountered in the home at work or casually The air borne substances listed above are the most frequent causes A reaction to animal danders may be caused by contact with animals or in the case of feathers by contact with pillows and upholstered furniture Contact with cotton seed and kapok is established by their presence in bedding Orris root rice powder and cornstarch are frequent ingredients of cosmetic powders Cereal flour acts rarely after ingestion, usually by inhalation and is, therefore a more common cause of the disturbance among cooks and bakers House dust is probably the commonest specific agent and the irritant seems to be different from all the known substances and as yet has not been identified The dust of hay or straw is distinct and bears no relation to their respective pollens It is an etiologic factor among farmers and those who sleep on bedding made of grass and straw Spores of fungi are unquestionably important They are especially prevalent in the summer and so may give a seasonal appearance to the coryza but since they do exist and may be isolated from the dust of houses at all times of the year they are properly classed as agents of perennial hay fever

In properly allergic cases acute upper respiratory infection or the exacerbation of a chronic sinusitis may cause typical attacks of vasomotor rhinitis Hyperplastic rhinitis and sinusitis with or without polyposis represent a special type of reaction to infection in allergic individuals

Treatment —The diagnostic tests are carried out by the scratch or intradermal methods used for seasonal hay fever It is particularly important in this type however to determine not only that an individual reacts to the test and that the reaction can be verified at will but also that the individual has actually come in contact with the reacting substance and that it is truly the exciting cause In other words one must differentiate between *actual* and *potential* excitants

The therapeutic principle best applied to the management of these cases is *strict avoidance of all contact with the actual excitants* If the reaction is to feathers all chance of contact with feathers must be removed Particular attention must be paid to cleanliness and the home should be kept as free from dust as possible At times change of occupation is required Foods if causative agents must be eliminated from the diet When contact cannot be avoided treatment by injection may be employed It must be continued for a long time *hence* the advantage of the perennial form of treatment that is injection every three or four weeks once maximal doses have been reached

Treatment of the infective type requires the special attention of the rhinologist Vaccine injections may help

Robert A Cooke

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ASTHMA

Definition —Asthma is dyspnea of a characteristic wheezy type caused by obstruction to the flow of air in and out of the lungs Such wheezy breathing occurs in a variety of conditions and may be either continuous or paroxysmal hence the term *asthma* should be used to indicate not a disease but a symptom *Bronchial asthma* is a term which is loosely applied to a syndrome exhibited by patients who between attacks of asthma are subjectively and objectively well

History.—Asthma was familiar to various Greek and Roman authors though the attacks of severe wheezing were confused with dyspnea of other causes In Sir John Floyer's "Treatise of the Asthma" published in 1698 there is an interesting account of his own symptoms Although John Bostock in 1819 discussed the effluvium of new hay as the cause of *Catarrhus Aestivus* and Blackley in 1865 demonstrated that itching swelling and edema followed the application of pollen to the skin of patients with hay fever and asthma the relation of the pollens animal danders and other dusts to the symptoms were not considered until the work of Dunbar in 1905 In 1906 Wolff Eisner demonstrated the specificity of pollens and initiated the study of pollen chemistry Von Pirquet's description of serum disease appeared in 1905

In 1910 Meltzer recognized that the symptoms and pathology of anaphylactic shock in the guinea pig were quite similar to those of asthma During the next few years many different authors described the symptoms which follow contact with particular proteins in susceptible individuals H L Smith's case of buckwheat poisoning was described in 1909 Schloss study in 1912 of a child sensitive to egg white and to almonds is classical In 1914 Goodale demonstrated that the application of horse dander to the turbinates causes an acute attack in horse asthmatics After that, Talbot Walker Cooke Longcope and others brought out the value of skin tests and clinical allergy became of practical importance in internal medicine

Incidence —Asthma is a common disease It occurs in individuals of all *ages* and *races* The *sexes* are about equally affected

Etiology —The causes of asthma are manifold They group themselves like the parts of a tree The trunk represents a fundamental basis which may be called the asthmatic state which explains why some individuals have asthma and others do not This trunk depends perhaps on several roots one of which we recognize as inheritance for it is known that in at least 40 per cent of cases someone in the family has had hay fever asthma urticaria or some peculiar susceptibility to a food or odor The other roots are unknown Upward the tree trunk divides into two main branches the first includes those individuals whose asthma is due to some cause outside of the body to which they are hypersensitive (the extrinsic group) the other includes those not demonstrably hypersensitive where the cause is apparently inside the body (the intrinsic group) Reports of the relative percentage of cases in the two groups vary greatly presumably because the clinical material varies in age and in the type of asthma predominant in different clinics More than 75 per cent of all asthma is extrinsic

Extrinsic asthma implies that the cause of trouble is some foreign substance to which the individual is hypersensitive The basic cause is allergy The occurrence of *occupational asthma* is evidence that hypersensitiveness is acquired presumably only by susceptible persons The precise cause thus depends upon environment

Hypersensitiveness is demonstrated in at least two ways (1) Clinically by showing that symptoms occur after contact with the offending substance (2) By skin test scratch or intracutaneous as will be described presently Eye tests and nasal tests are sometimes used

In extrinsic asthma contact with the foreign substance may be brought about by inhalation by ingestion or by injection into the skin Of these various methods inhalation *of dusts* is by far the most important in

adults, while ingestion *of foods* plays the important role in children Injection is mentioned because *in the specific treatment of* hay fever, asthma may be produced by an overdose of pollen extract

DUST ASTHMA (BY INHALATION) has many *causes which can be divided* into groups The first is that of *pollens* Trees grasses and weeds may each and all be important but their relative value depends on locality In *southwestern United States* the pollen season is long with grass pollen in the air almost all the year In New England the season is shorter Trees produce pollen in *quantity but each one only for a few days* in the month of May Tree pollen asthma is rare although it may be severe Grasses begin to pollinate in late May and grass *pollen is demonstrable in the air until after* August 1st Many patients have hay fever and asthma from grasses Ragweed is abundant east of the Rocky Mountains and its *varieties cause much trouble in August and* September and until after frost

MOLDS notably the fungi of the imperfect genera produce spores in large quantities *especially in the late summer and fall and* it is quite likely that these play a part in certain complex cases

DANDERS AND EMANATIONS FROM ANIMALS *constitute another important group of* etiologic agents Fur is sometimes as bad as the living animal itself Feathers in pillows are important

OCCUPATIONAL DUSTS constitute an important group Bakers and housewives may have asthma from wheat flour Cotton, wool leather malt orris root ipecac flaxseed and glue have all been described as causes of asthma and the list grows with the development of complex chemicals used in modern industry Dyes solvents bleaches developers fixatives and other substances may cause allergic symptoms usually of the skin Occasionally they cause asthma

HOUSE DUST represents from the practical point of view the greatest source of trouble Many patients have been cured of asthma by the elimination of kapok called silk floss in pillows mattress and over stuffed furniture Cotton dust is less important Curled horse hair is safe in almost all instances, for patients with frank horse asthma can sleep on a horse hair mattress without difficulty The new mattresses made of sponge rubber are promising

FOOD ASTHMA (BY INGESTION) is not common except in children The important offending foods are the common foods—eggs wheat and milk After these three the other foods or drugs cause trouble in only occasional cases It is difficult to prove clinically that one food is more responsible than another for the asthma a fact which perhaps explains the confusing reports in the literature

Multiple sensitiveness is the usual rule and patients may be sensitive not only to a pollen and to an animal dander but also to some article of food and all at the same time

Intrinsic asthma is a term which implies *that the cause of trouble is inside the body* the patient carries it with him regardless of changes in season residence occupation or diet This is the difficult group which we describe as dependent upon some X *factor'* In this group 20 out of 283 patients (7 0 per cent) have died of asthma, whereas in the extrinsic group no death from asthma *has occurred There are several* types of cases

1 Intrinsic asthma may develop on a *background of extrinsic asthma*—the attacks *becoming more frequent* and more severe until the patient is no longer relieved by a change in environment or by admission to the hospital

2 HEAD COLDS LEAD TO ASTHMA —Children who wheeze with colds are often slightly sensitive to some dust substance and the cold makes the subclinical sensitiveness effective In older persons the term asthmatic bronchitis is descriptive the attack depends upon a true bacterial allergy Adults with varying degrees of emphysema or chronic bronchitis have severe asthma with every cold On the other *hand* severe infections with fever like pneumonia may cause asthma to disappear at least temporarily a fact which is of considerable theoretical importance

3 A SUDDEN ONSET OF INTRINSIC ASTHMA may occur after the age of forty five more often in men than in women It may follow an acute *respiratory infection* or it may come without obvious cause This group is hard to treat In the hospital these patients

improve but they do not show the dramatic change exhibited by those extrinsic cases which have escaped from a dust which was causing trouble at home

4 CHRONIC PERSISTENT VASOMOTOR RHINITIS sometimes leads to asthma and so creates a systemic disease of serious prognosis

In intrinsic asthma the cause may lie not in the respiratory tract but in some other part of the body Thus

REFLEX CAUSES arise from lesions in the nose and sinuses About one half of our cases of intrinsic asthma are found to have lesions of the paranasal sinuses varying from thickened membrane to a full blown pansinusitis of the polypoid type and most of them have already had operations on nose or sinuses obviously without relief The high proportions are good evidence that these lesions are part of the picture of asthma and not a cause of it Nevertheless there are a few cases in which operations on the sinuses or even the removal of nasal polypi have brought prompt relief Furthermore there is evidence that a true nervous reflex can exist with the afferent impulses arising in scar tissue in the region of the sphenopalatine ganglion

TOXIC CAUSES arise from focal infection We have seen patients quite relieved of chronic asthma by operations on the appendix or gallbladder or pelvic organs as well as more commonly by the extraction of abscessed teeth or by tonsillectomy Constipation *as a cause belongs in the same category* Also to be included are the rare cases with a positive Wassermann whose asthma clears with antisyphilitic treatment

NEUROTIC CAUSES probably exist Cobb and his associates have described several patients in whom the history and course were so bizarre as to preclude any explanation other than a neurosis On the other hand we see many patients who appear nervous and apprehensive with their asthma but who have become normal again when more careful study has resulted in the elimination of the feather pillow some toilet powder or a household pet In these cases the nervousness is presumably an effect of the asthma and not the cause of it In a few cases however nervousness with the poor hygiene which goes with it may account for the whole picture In children treatment by such simple measures as a mid-day rest a glass of milk between meals more outdoor air, less sympathy and better discipline from the mother have been enough to relieve the symptoms even without changes in diet or environment In certain adults the onset of asthma has coincided with a severe emotional strain and such cases have been difficult to treat especially if there was also a marked physical strain as might be produced for example by a long illness and death in the family

CARDIAC ASTHMA AND RENAL ASTHMA are terms descriptive of the underlying cause in a few cases but as pointed out by Harkavy diseases of the heart and arteries may coexist with asthma the cause of which is entirely separate and independent

Whatever the original cause of asthma *secondary infections of the bronchial mucous membrane* are prone to develop Pollen asthma which ordinarily is relieved by the first frost of autumn may because of a secondary infection continue into the winter

Morbid Anatomy and Physiology—The symptom asthma depends upon an obstruction to the flow of air in and out of the lungs This may be due either to a spasm of the bronchial muscles to edema of the bronchial mucous membrane or more important to masses of sticky mucus in the bronchial lumen

The bronchial muscles are arranged spirally to form a lattice like structure around *the tubes as Miller has described Asthma* may be due either to the contraction of this lattice structure and the consequent closing of the small bronchiolar openings between its fibers or it may be due to the contractions of the minute sphincters about the infundibula More recently T B Mallory has found that in patients dead of asthma the entire bronchial tree is filled with tough sticky exudate which can be pulled out in long rubbery strands The plug has a fairly definite structure there is little or no reaction in the surrounding lung no evidence of infection and there is an increase in the number and size of the mucous glands an expression of the overactivity of these glands which results in the outpouring of excessive secretion into the bronchial lumen

The physicochemical mechanism by which

asthma is produced is so far unknown Whereas the clinical picture is relatively uniform, it is brought about by a wide variety of exciting causes The asthma due to extrinsic factors—pollens animal danders, kapok, house dust and even foods—appears to be a single disease entity and therefore, one thinks of a common mechanism Histamine as the intermediary factor has been suggested for three principal reasons (1) the injection of histamine into normal animals or man can produce asthma (2) Lewis



Fig 45—Cut section of lung from case of bronchial asthma *Note the tough white plugs protruding* from many of the larger bronchi Note also the scattered white slightly elevated areas representing plugs in the smaller tubes The whole lung is emphysematous and of uniform texture

has produced circumstantial evidence that injuries can cause many cells to release the histamine like substance which they normally contain and (3) Weiss and others have shown that *patients with asthma react* more violently to the intravenous injection of histamine than do normal persons Hence the theory that the specific antigen antibody reaction called allergy taking place on the surface of cells results in the release of histamine which in turn causes the stimulation of bronchial muscles and glands to produce asthma Other substances beside histamine could fill the same function Acetylcholine is also a normal constituent of cells and there may be other substances with similar attributes The histamine theory is interesting because the same mechanism can be invoked by exciting agents other than allergens The writer believes therefore that allergy is an important cause of asthma but that it is not the only cause

In the production of reactions in passively sensitized skin sites it has been shown that the reaction is obtained regardless of whether the antigen is inhaled (Cohen) ingested (Walzer) or injected into a contralateral site (Gay) These experiments help to explain food asthma on the same basis as pollen or dust asthma the antigen does not reach the cells by direct inhalation it is absorbed through the nose or stomach and enters the blood stream

Meantime it seems that asthma occurs only in certain individuals predisposed to it by inheritance or otherwise The increased *susceptibility to histamine suggests* a possible mechanism by which this predisposition may be expressed The point is that the problem of asthma probably lies more in the domain of physiology and chemistry than in that of immunology

The clinical picture of asthma is not limited to the pulmonary symptoms *Lesions of the paranasal sinuses* are part of it Thickened membrane polypoid sinusitis *purulent* sinusitis are all too common in the clinic and so whatever mechanism is found to explain asthma must explain sinusitis as well The latter is the result of the process and only rarely the cause of it *Eosinophile cells* in the blood sputum and nasal secretions are likewise characteristic of asthma In the blood the count may be as high as 50 per cent of the total leukocytes Eosinophilia may occur in both extrinsic and intrinsic cases and both during and between attacks In one group of very unusual cases studied by the writer the blood eosinophils were well over 50 per cent there was evidence of lesions of the blood vessels in addition to lesions of the bronchial and nasal mucous membranes The diagnosis of periarteritis nodosa was made and confirmed by biopsy and autopsy *Vascular lesions* may be another part of what can now be called the

asthmatic syndrome *Emphysema* is always present In most cases it is temporary, the process is still reversible but sometimes the barrel shaped chest the presence of em physematous blebs on the pleural surface and the development of chronic cyanosis show that emphysema has become a serious complication *Heart disease* is not common but there may develop a cor pulmonale or pulmonary heart disease sometimes called the emphysema heart due to increased resistance in the pulmonary circulation Hypertrophy of the right ventricle develops slowly and insidiously and when failure comes there is engorgement of the entire venous system with deep cyanosis polycythemia and other signs of decompensation

Symptoms —Bronchial asthma is characterized by wheezy breathing For example the patient with horse asthma goes into a stable Within a few minutes his eyes itch his nose runs and soon he coughs feels a tightness in his chest and breathes with difficulty The asthma thus induced may pass off in a few minutes or it may develop into a distressing picture forcing the patient to sit with his elbows on his knees and his head down so that every accessory muscle of respiration can be brought into action The expiration becomes long and noisy the inspiration difficult and with obvious effort The attack may last for many hours but when it is over he will be free so long as contact with horses is avoided

Patients with intrinsic asthma present a similar picture except that the onset and remissions are less abrupt and the attack once started may continue for days sometimes for weeks Exertion cold air dust or fumes aggravate the symptoms The patient may awaken from one to four times at night to cough and wheeze until relief comes through medication Occasionally he must spend the whole night in a chair in front of a small table over which he can lean and sleep between the paroxysms

Cough varies according to the amount of bronchial infection but at the end of the attack cough with the production of sticky sputum is characteristic *Sputum* varies in character according to the extent of secondary infection Cultures show organisms of all sorts with staphylococci predominating in the purulent varieties Influenza bacilli are also found in the thick sputum of patients with long standing bronchial infections Eosinophilic cells are characteristic features of asthmatic sputum *Hemoptysis* does not occur in simple asthma but is not rare in emphysema *Pain* is not common except as excessive cough and severe asthma produce a sore chest *Gastro intestinal* symptoms are rarely noticeable except in a few patients who are sensitive to foods Patients cannot eat during severe asthma and hence they usually lose weight

Physical examination in the typical extrinsic case without secondary infection shows rales which are dry musical and evenly distributed In other cases an uneven and variable distribution of moist rales indicates bronchial infection Loud bubbling rales heard in certain areas suggest plug formation Diminution of the breath sounds is the rule In emphysema the chest outline may be barrel shaped the percussion note is loud the lung bases appear to be low and the heart outline small because of the distention of the overlying lung *Cyanosis* is not present in simple asthma but occurs in patients with emphysema and bronchitis who suffer from a markedly increased dead space in the air passages Marked cyanosis is an important symptom of *cor pulmonale* when the right heart breaks under the excessive strain The *blood pressure* is normal but the systolic pressure often falls sharply during inspiration because of the increased negative pressure in the pleura during inspiration In the *blood* eosinophilia is characteristic The fasting blood sugar content and the sugar tolerance curve are both normal in asthma

Diagnosis —The diagnosis of asthma is usually made by the patient Between attacks there may be no evidence of disease but during attacks the wheezy dyspnea is so characteristic that diagnosis can be made on sight The long arduous respiratory phases cannot be confused with the dyspnea of pneumonia or cardiac failure

Asthma however is merely a symptom To find the cause of it there are three steps The first and most important is the *history* and in taking the history there are three essentials The first is to use dates in an orderly chronological record which should begin with the first wheeze The second is

asthma is produced is so far unknown Whereas the clinical picture is relatively uniform, it is brought about by a wide variety of exciting causes The asthma due to extrinsic factors—pollens animal danders kapok house dust and even foods—appears to be a single disease entity and therefore one thinks of a common mechanism Histamine as the intermediary factor has been suggested for three principal reasons (1) the injection of histamine into normal animals or man can produce asthma (2) Lewis



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the sulfate or the hydrochloride is helpful in the mild cases but may cause insomnia The inhalation of smoke of stramonium leaves the chief constituent of most commercial asthma powders and of asthma cigarettes often relieves the bronchial spasm and the edema Certain sprays for the nose and throat are also helpful Steam plain or medicated with tincture of benzoin may be inhaled Morphine should never be used Morphine itself gives a skin test in normal people it is a cholinergic drug and as such tends to increase the bronchospasm It may inhibit the respiratory center to a dangerous degree

To avoid drug allergy it is best to use drugs with simple chemical formulas The bromides chloral hydrate and paraldehyde are all useful Cathartics must be restricted to the various salts

Severe intractable asthma requires more strenuous measures If possible the patient should be moved to the clean environment of a hospital and preferably to a dust free room If epinephrine is not effective subcutaneously it can be given intravenously adding 1 cc of the 1 1000 solution to a liter of salt solution preferably with 5 to 10 per cent of glucose and taking at least an hour for the injection It should be remembered that too much adrenalin can cause auricular and perhaps ventricular fibrillation Aminophylline in doses of 0 25 Gm dissolved in 10 cc of water is often very effective when injected intravenously Aminophylline is also effective when given by rectum A dose of 0.50 Gm dissolved in 20 cc of tap water can be given each night if necessary Ether in olive oil an ounce of each mixed together and given by rectum is recommended and ether by inhalation to full anesthesia may abolish the paroxysm

The inhalation of helium with oxygen has been found effective in terminating intractable asthma Due to the low atomic weight of helium and the decreased pressure required for its transport through small orifices the effort of breathing becomes greatly diminished Barach recommends that a mixture of 20 to 35 per cent oxygen in helium be given by means of a mask or better a helmet hood in which a positive pressure of 3 to 5 cm of water is maintained by the pressure tank If anoxemia is marked the percentage of oxygen can be increased to 35 per cent Barach describes the advantages of producing bronchial relaxation' several times a day and he accomplishes this by three procedures Aminophylline is given by rectum The patient inhales as deeply as possible a fine spray of epinephrine in strong 1 to 100 dilution and then is given the oxygen helium mixture to breathe for periods of from one to four hours or until relief is obtained Straight 100 per cent oxygen is also very useful in desperate cases and can be employed for as long as twelve hours without harm The B L-B mask devised by Boothby and others is useful and efficient

Bronchoscopy to remove the sticky bronchial plugs by direct suction may be life saving in properly selected cases

A high fluid intake is always important and fluids should be given by vein or rectum if they cannot be taken by mouth

The Cause.—The discovery and elimination of the specific cause are in the present state of knowledge the chief objects of treatment The importance of kapok in cheap mattresses pillows and furniture has been described above Changes in bedding may lead to striking results The removal of animals face powder or rugs has brought relief in various cases Allergic cleanliness becomes necessary It applies to those items which are dust producers as well as to those which are dust catchers The laboratory worker sensitive to rabbits and guinea pigs remains free from attacks as long as he stays away from the animal room A patient with food asthma may be cured by elimination of the offending substances from the diet Rowe lays great stress on food even in patients whose skin tests to food allergens are negative and his elimination diets have been very effective in his hands They exclude the three foods which give the highest percentages of positive reactions—eggs wheat and milk It is proper to observe however that when wheat is taken from the diet a reduction of total carbohydrate usually results automatically and the writer believes that this change in the diet may well be important in modifying the fundamental background of the allergy

When the patient cannot escape the offending substance—the pollens in the hay fever season or the dusts in his industry—

to account for all the time It is often quite as *important* to know when and why the attack ended as to know when and why it began If there was a free interval without asthma the fact and the dates should be written down The third is to include the *dates of changes in residence* or *occupation* and the dates of operations or intercurrent diseases among the other dates of changes in symptoms When this is done the whole story can be seen in its broad aspects Two *small children both had asthma in summer*, in one the attacks began before the move to the seashore it was due to pollens In the other, asthma began on the first night of the move it was due to the kapok mat tress *in the summer cottage*

The second step is the *physical examina tion* The patient must be studied as a whole His size color nutrition and posture should all be noted What other disease is present besides asthma? Has he fever or cyanosis? The nose is important In hay fever the mucosa is swollen and pale A deviated sep tum may prevent the drainage of sinuses Nasal polypi indicate trouble and trans-illumination and x ray may show clouding in the sinuses All foci of infection not only in the head but in the abdomen and pelvis should be recognized promptly Pregnancy visceroptosis malnutrition syphilis and tu berculosis need only to be mentioned to em phasize the importance of treating the pa tient first his asthma second

The third step in diagnosis is the skin test The cutaneous or scratch test is easy to apply Powders or solutions are dropped on the skin and small scratches are made through them The intracutaneous method *is* much more delicate but requires a careful technic Sterile solutions in known concen tration are injected into the skin itself The solutions must be active so as to *give posi* tive tests in persons known to be sensitive and they must be nonirritating and give no reaction in normal persons With both meth ods a positive reaction consists of a wheal and *erythema* which appears within twenty minutes Controls are necessary and several tests with various substances should be ap-plied at the same time one to *control the* other When all the tests react the patient *is* said to have an irritable skin unless per haps the syringes or extracts are dirty chem ically while being clean bacteriologically In our clinic, a separate syringe is reserved for each extract used

Discrepancies between tests and symp-toms are all too common Positive tests may be found but with no symptoms to go with them They often represent the past history rather than the present illness The patient may have had hay fever previously but now only the positive skin test remains Nega tive tests in the face of a true clinical sensi *tiveness* sometimes occur *In* occasional cases, we have found that a retest later is positive so it would appear that sensitiveness devel ops in different tissues at different times Possibly this explains the finding of positive *eye (conjunctival) tests in a few patients* whose skin tests are still negative When discrepancies occur it is well to be guided by the history rather than by the skin test On the whole however, symptoms and skin tests are *consistent* in most cases

Tests to be of diagnostic importance must be correlated with the history in such a way as to make a logical and reasonable explana tion of the attacks Clinical experiments made either by changing the environment or by modifying the diet are frequently nec-essary before positive tests can be inter-preted

Prognosis —Patients with extrinsic asth ma do not die of asthma except in those rare cases in which an overdose of the spe-cific substance injected for test or for treat *ment has led by accident* to a very severe allergic reaction In the intrinsic cases how ever death from asthma has occurred in 7 6 per cent of cases

The hope of permanent relief depends entirely upon the discovery and the removal of the cause Whether the fundamental con stitutional basis for the allergy or for the *asthma can be modified or not is* so far quite doubtful Children particularly boys who develop their symptoms early have the best chance of outgrowing their trouble

Treatment —*The Attack* —The treat ment of an attack is usually simple Adren alin chloride injected subcutaneously can control almost any attack for a time varying *from minutes to hours* A dose of 0.25 cc of 1 1000 solution often works as well as 1 cc and the dose can be repeated at half hour intervals if necessary *Ephedrine either* a-

study of the clinical and immunologic phenomena of serum sickness was undertaken by von Pirquet and Schick their results were published in a monograph in 1905 Their work defined and illuminated the problem and has stimulated many others during the past thirty five years to investigate the incidence symptomatology and mechanism of serum reactions

Incidence.—Not every patient treated with serum develops serum sickness If amounts below 10 cc are used only about 10 per cent have symptoms but if 100 cc or more are administered only 10 per cent escape at least some manifestation of serum sickness The incidence therefore depends largely upon the amount of serum given but also in lesser degree upon other factors the preparation of the serum the horse producing the serum and the patient himself Race is also a factor Negroes and American Indians appear to be less susceptible than the white race Age sex the disease for which serum is given and the route of administration seem to have little or no effect on incidence The recent introduction of refined and concentrated therapeutic sera from which the serum albumin has been eliminated has because of the smaller amount of foreign protein injected caused a reduction in the incidence of serum sickness

Pathogenesis.—Precipitins for the foreign serum are usually in the circulation after the ninth or tenth day In severe cases they are apt to reach a high titer and in patients who despite large amounts of serum have little or no serum sickness they are usually absent *transitory or of low titer* When the precipitin in the circulation reaches a high titer the foreign serum still in the circulation disappears rapidly when no precipitin is demonstrable the disappearance of the foreign serum from the circulation is greatly retarded The symptoms of serum sickness are thought to be due to a union of the foreign serum with the specific precipitin which has been elaborated during the incubation period In addition to horse serum precipitins agglutinins and lysins for sheep cells appear in the blood of patients treated with horse serum The constituent of serum chiefly responsible for serum sickness seems to be the pseudoglobulin the euglobulin may also participate in the production of the symptoms the albumin fraction is apparently inactive

Symptoms—When serum is administered to an individual for the first time there is usually an incubation period of six to twelve days before the onset of serum sickness The incubation period may in rare cases last two or even three weeks In a small percentage of patients the incubation period may be less than six days, but in such patients it is not always possible to exclude the possibility of a previous and forgotten injection of serum such as an immunizing dose of antitoxin or toxin antitoxin injections in childhood Some of these individuals with shortened incubation period may have a spontaneous hypersensitiveness to horse serum of such low degree that neither a skin test nor the history reveals the hypersensitiveness

When large amounts of serum are administered the *severity of the symptoms* is determined chiefly by the constitutional susceptibility of the individual A liter of serum given during the course of two or three days may produce nothing more than a few urticarial wheals and slight enlargement of the superficial lymph nodes for a day or two Other patients after receiving a few cubic centimeters of serum may have severe urticaria edema fever arthritis and swollen tender lymph nodes for one or two weeks Exceptionally the symptoms persist for three weeks or longer In a large proportion of patients they subside in less than a week When such amounts of serum as are commonly employed in diphtheria and tetanus immunization have been administered the severity as well as the incidence of symptoms tends to be less than after the large amounts given for pneumonia and meningococcus meningitis But even after small quantities of serum given subcutaneously an occasional patient may have severe and prolonged serum sickness

Serum sickness without *skin manifestations* is very rare The eruption is usually urticarial or a mixture of urticaria and erythema Itching of the skin often comes first, then patches of erythema and discrete wheals appear the wheals with a circumferential zone of erythema may remain discrete or as the eruption becomes more intense large wheals the size of the palm of the hand appear and by confluence form bizarre patterns over the chest back or ex

specific desensitization can be attempted by giving a series of inoculations with the corresponding extract The technic is difficult the dosage is hard to gauge and general constitutional reactions sometimes of considerable severity are prone to occur Furthermore it is our experience that the desensitization produced is usually relative and temporary The extract used should contain the specific substance which has caused the symptoms

The cause of intrinsic asthma is unknown but much can be done to relieve the patient The removal of focal infections in teeth tonsils sinuses gallbladder pelvis and even prostate has helped various individual cases The *relation of paranasal sinusitis to* asthma has already been discussed Sinus operations have helped a few cases usually for a temporary period, but the later results are often disappointing Nevertheless it is important to secure nasal drainage by removal of polyps and other simple procedures but it is also important not to disturb the normal structure and function of the nasal mucosa

Injections of nonspecific substances like peptone milk crotalin, the patient s own blood, and various vaccines are often helpful Good results seem to go hand in hand with the production of a local reaction at the site of inoculation Such treatment is capable of aggravating the asthma just as mild respiratory infections may Severe infections, however, such as pneumonia are *always followed by a temporary disappearance* of the asthma hence one form of treatment is to raise the temperature artificially by radiant heat or short wave or by giving typhoid vaccine intravenously Fever therapy is a rather drastic form of treatment for the asthmatic and not without danger

Potassium iodide is always useful in asthma It stimulates expectoration and so modifies the formation of tough sticky plugs Sometimes however it stimulates to the point of irritation and so may do harm Vitamins and hormones have each and all been considered and tested but so far with little success Acids and alkalis have both been given with doubtful results Deep x ray therapy has brought improvement to an occasional case The operations of sympathectomy and of vagectomy are disappointing

Finally, it should be said that whereas treatment of the asthma is important treatment of the patient as a whole is more important For asthma, the physician must be a doctor in every sense

FRANCIS M RACKEMANN

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SERUM SICKNESS

Definition —Serum sickness is an allergic reaction resulting from the parenteral administration of a foreign serum and characterized by an incubation period skin eruptions enlargement of lymph nodes fever edema and polyarthritis It should be distinguished from the immediate shocklike *and sometimes fatal reactions which occur* when foreign serum is administered parenterally to an individual who is hypersensitive to the serum employed These *latter* reactions are better called serum accidents Individuals slightly sensitive to horse serum may exhibit transition forms which present themselves as delayed serum accidents or as serum sickness with shortened incubation period

History —Although animal blood had occasionally been used in transfusions since the seventeenth century and various untoward effects noted not until 1875 (Landois and Ponfick) was there any appreciation of the important difference between human and animal blood for transfusions Generalized urticaria ten days after transfusion of alien blood was reported in 1874 (Dallera) but its significance was not understood *When diphtheria antitoxin* came into general use in 1890 the symptoms of serum sickness and serum accidents soon attracted widespread attention At first they were ascribed to the antitoxin content and then to some other unknown constituent of the horse serum but Johannessen (1895) showed *that normal* horse serum was equally effective The first systematic

ent serum proteins occurs at different times, and Coca found no relapses in 120 patients with serum sickness due to a diphtheria antitoxin consisting of the isolated pseudoglobulin

Diagnosis—Very rarely is there any difficulty in recognizing serum sickness Occasionally a relapse with an atypical or inconspicuous eruption may cause uncertainty It is sometimes difficult to decide whether fever occurring during or immediately after a serum eruption is due to a complication of the disease for which the serum was given or to the serum sickness A leukocyte count below 12 000 or an eosinophilia is in such cases evidence in favor of serum sickness

Prognosis—Fatalities from serum sickness itself are unknown Complete recovery, even from the severe forms is almost invariable provided the infectious disease for which the serum was administered leaves no permanent ill effects A high percentage of individuals retain for years some degree of sensitization to the serum employed yet with proper precautions the same kind of serum can be administered subsequently to nearly all of these patients

Rare neurologic complications such as neuritis polyneuritis transitory mono or hemiplegias have been described mainly by French observers

Treatment—It has not been demonstrated that serum sickness can be prevented Calcium and histaminase seem to be useless A certain amount of symptomatic relief is the most that can be expected For the pruritus calamine lotion containing 1 per cent phenol is often helpful Bicarbonate of soda baths may give temporary relief in severe cases Hypodermic injections of epinephrine (0 3–0 6 cc of the usual 1 1000 dilution) will usually give transitory relief from the pruritus Ephedrine (0 025–0 05 Gm) given by mouth three times a day before the onset of symptoms appears also to mitigate the symptoms Derick Hitchcock and Swift have shown that antirheumatic drugs given in adequate doses (6–10 Gm a day) from the time of the serum injections will keep the antihorse precipitin in the patient s serum at a lower titer than would otherwise be the case and will also prevent or lessen the severity of the arthritis

George M Mackenzie

SERUM ACCIDENTS

Definition—Serum accidents are the immediate shock like sometimes fatal reactions which occur after the parenteral administration of a foreign serum

Etiology—The essential cause of these reactions resides in the specific reactivity of the individual Persons susceptible to asthma or to rhinitis and coryza when close to horses are most likely to have serious serum accidents Those sensitized by a previous injection of serum may also have alarming or, rarely even fatal reactions but in general are less sensitive than the horse asthmatic group Certain individuals also who have never experienced symptoms from contact with horses and who have not received a previous injection of serum show positive skin reactions to horse serum and hence must be considered hypersensitive Very rarely even the intracutaneous test for sensitivity may if the individual is highly sensitive and the test solution is not sufficiently dilute cause an immediate fatal reaction

Pathogenesis—Despite certain dissenting opinions most competent authorities look upon serum accidents as examples of anaphylaxis The fact that the majority have occurred in spontaneously hypersensitive individuals upon the first injection of serum has been urged as a reason for separating this group of serum reactions from anaphylaxis In those cases in which the first serum injection is tolerated without immediate symptoms and a subsequent serum injection after weeks or months has unloosed immediate and violent symptoms the analogy with experimental anaphylaxis is nearly complete The chief discrepancy is found in the phenomenon of desensitization

Pathology—Postmortem examinations have shown inflated voluminous lungs with acute emphysema and rupture of the inter alveolar septa the viscera are congested small hemorrhages into the myocardium and the adrenals and into the interstitial tissues of the lungs and kidneys have been described The right ventricle is apt to be greatly distended with blood and the left ventricle contracted and empty Efforts to incriminate the thymus in these fatal serum accidents have been based on tenuous evidence

tremities The face is usually affected Itching is often intense Occasionally the eruption is morbilliform or scarlatiniform but these atypical varieties are more often seen during a relapse than during the *initial sickness* Purpuric rashes are occasionally observed in serum sickness of more than average severity The eruption usually disappears after three to five days When the serum has been administered subcutaneously or intramuscularly the earliest eruption is apt to be at the site of the injection It may *remain confined* to this area—the so called 'local serum sickness —or subsequently become generalized

Slight or moderate enlargement of the *superficial lymph nodes* is usually present Often this *is the first symptom antedating* the eruption by one or two days The nodes may or may not be tender Frequently the epitrochlears are the first nodes in which the enlargement can be felt After the other symptoms of serum sickness have subsided the nodes often remain enlarged for several days When the serum has been administered *under the skin or into the muscles* the regional nodes are apt to be the first to increase in size Slight enlargement of the spleen is not infrequent

After large amounts of serum 50 to 60 per cent of patients with serum sickness show some evidence of *arthritis* In most cases objective changes are slight or absent The patient *complains of pain and stiffness* but there is little to be seen or felt In a small proportion of cases the joints are swollen hot red and distended with an exudate which has an interesting similarity to the joint fluid of rheumatic fever (Swift and Boots) It is turbid and contains leukocytes up to or above 20 000 per cubic millimeter *Polymorphonuclear* cells usually predominate A precipitin test often reveals the presence of horse serum in the joint exudate The commonly involved joints are the knees ankles elbows wrists and small joints of hands and feet Less commonly the other joints are affected The temporomaxillary joints are involved more often in serum sickness than in rheumatic fever It is unusual for joint symptoms to appear at the onset of serum sickness

Fever occurs in about one third of the cases From an elevation of only 1° F for a day or two all graduations are observed In severe cases the temperature *may reach* 103° or 104° F every day for a week or ten days There is no constant or typical temperature curve Frequently it is very irregular and remittent

Edema occurs also in about one third of the cases, it is more frequent in children than in adults The face sacral and pretibial regions ankles *hands and arms are the* areas where it is most often noted Chloride and water retention a lowered phthalein excretion moderate oliguria albuminuria and cylindruria are not unusual concomitants of the edema Rarely if ever is there a measurable *nitrogen retention* After the serum sickness has subsided all evidence *of impaired renal function vanishes* Attempts to demonstrate horse serum in the urine have been unsuccessful *Optic neuritis* with a slight increase of the cells and globulin in the spinal fluid may be observed occasionally Neuritis and other disorders of the nervous system occur in rare instances

In adults there is frequently no change in *the blood picture Von Pirquet and* Schick found that children show a leukocytosis during the incubation period and leukopenia after symptoms develop Such changes rarely occur in adults Even severe cases may show nothing abnormal in the blood count or there may be a slight leukocytosis while symptoms are present and toward the end or *after the period of symptoms* an increase of the eosinophile cells The sedimentation rate is usually unaltered

Other symptoms occasionally observed without any other explanation than that they are a part of the serum sickness are abdominal pains vomiting diarrhea stupor headache conjunctivitis and sore throat

Relapses occur in our experience after a free interval of from four to fourteen days With a recurrence of symptoms the eruption *is more apt to be erythematous* morbilliform or multiform than urticarial Any of the other symptoms may be present There are two observations supporting *the belief* that relapses represent reactions to antigenic constituents of the foreign serum different from those responsible for the initial *out*break of symptoms Dale and Hartley showed that when an animal is sensitized to a foreign serum sensitization to the differ

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ANGIONEUROTIC EDEMA

Definition—Angioneurotic edema is characterized by transient circumscribed edematous swelling of the skin or mucous membrane *occasionally of the viscera Individual* lesions persist from a few hours to a few days and may occur either without sensory phenomena or with itching burning or prickly sensations One form is hereditary and frequently terminated by a fatal edema of the glottis another form is relatively benign and in some cases is dependent upon a *demonstrable food allergy Urticaria and* angioneurotic edema are frequently associated

History.—Under the title akutes umschriebenes Hautodem Quincke in 1882 described the nonhereditary form. Priority has usually been assigned to him although Milton in 1876 described the same condition under the title of Giant Urticaria" The first descriptions in American literature were from Osler who reported a *remarkable family history in which the disease* was transmitted for five generations

Incidence—The condition is not rare Bulloch in 1909 collected 170 cases from the literature

Etiology—*From Quincke s time* belief in an angioneurosis as the important pathogenetic factor has persisted and certainly in many of these patients psychologic difficulties *appear to participate in the etiology* Recent evidence makes it probable that in some of the *nonhereditary* cases the condition is due to *food allergy* The offending food can however be discovered only ex*ceptionally from skin reactions* these usually yield no helpful information This form is frequently associated with urticaria Focal infection and endocrine disturbances have been thought to be etiologic factors in some cases but critical scrutiny of the evidence in any series of these cases leaves a large percentage in which the etiology must be said to be undetermined *The sexes* are about equally affected No age is immune but *onset* at puberty has been noted in numerous cases The *hereditary form* of the disease may be transmitted through several gen*erations by both affected and unaffected* individuals without sex linkage The families studied do not show transmission according to the theoretical expectations of a Mendelian dominant It has been suggested that urticaria and angioneurotic edema are dependent on the same mechanism that in the former the superficial vessels of the skin are affected and in the latter the deeper vessels The mechanism which produces both of these cutaneous reactions seems to consist of vasodilation and transudation, the vasodilator substance is probably histamine —*free or in loose combination*—*or a hista*mine-like substance The mechanisms involved in wheal formation have been thoroughly studied by Lewis Recently Rose has reported a marked diminution of the histamine content of the blood when acute symptoms of angioneurotic edema were present

Symptoms—The *swellings appear as it* were spontaneously An itching prickly or burning sensation may precede the appearance of a smooth rounded elevation varying in size from a few millimeters up to large areas covering nearly the entire back The swellings may be tense and elastic or soft and pitting The skin may not change in color over the swelling *or may become pink* or dusky red Areas commonly involved are the lips the skin about the eyes chin hands feet, and tongue but any portion of the body surface may be affected A swelling may persist several days but more frequently dis

Symptoms —The onset of symptoms may be lightning like Almost before the needle is withdrawn local itching and edema develop A feeling of apprehension generalized urticaria often sneezing and a prickly sensation of the throat edema of face, hands neck or perhaps of the whole body cyanosis, choking sensation, cough and violent asthma are common symptoms The pupils dilate the pulse becomes thready or imperceptible, the temperature rises, convulsions may occur and the patient may be *dead* in less than ten minutes, in other fatal cases several hours may elapse between injection and death If the serum accident does not terminate fatally, the symptoms may become those of serum sickness at once or after a free interval of several days Other types of immediate untoward reactions to serum are (1) a thermal reaction characterized by an abrupt rise in temperature with or without a chill or chilly sensations (2) a shock like syndrome characterized by rapid weak pulse cold moist skin and low blood pressure without the more characteristic symptoms of the type of serum reaction commonly believed to be anaphylactic An abrupt fall of blood pressure is a frequent early sign of an impending serum accident

Treatment —The prophylaxis of serum accidents consists of (1) recognition before administering serum of those who are hypersensitive (2) desensitization of hypersensitive individuals

A history of asthma or hay fever should make one extremely cautious in giving serum particularly if the patient has experienced such symptoms when near horses or in stables A history of previous serum administration also calls for precautionary measures An intracutaneous test with a 1 10 solution of horse serum should always be made If this is positive the patient should be considered an unsafe subject for serum therapy by routine methods

Desensitization offers a method of administering serum safely to many patients who would otherwise react violently or even fatally if the whole amount of serum were injected in the usual way The genuine 'horse asthmatic *is often so highly sensitive* that he cannot be desensitized with such individuals even minute amounts of horse serum may endanger life but most of those whose hypersensitiveness dates from a previous serum treatment can in the course of twelve to twenty four hours be rendered sufficiently tolerant to take therapeutic quantities without danger If there is a history of asthma or a strongly positive skin test, the first desensitizing dose should be given *subcutaneously* Beginning with 0 005 to 0 025 cc according to the intensity of the skin reaction the dose may be doubled every half hour until 1 cc is given *Then 0 1 cc is injected intravenously* Dilution with normal salt solution is advisable because thereby injection may be made more slowly

The *intravenous* dose should be doubled every twenty to thirty minutes until the required amount has been given In case anything more than a mild reaction occurs one should wait the usual interval or longer and then repeat the last dose which produced only a mild reaction or none at all With some patients the desensitization program may be carried to a certain point but no further reduction of the dosage and subsequent gradual increase result in a reaction when the dose which previously caused a reaction is reached and repetition of this dose four or five times may be followed each time by a general reaction

If the serum is to be administered *intraspinally* the same procedure should be carried out until 5 or 6 of the intravenous doses have been given Then with diluted serum the intraspinal route may be tried slowly and cautiously With patients only slightly sensitive, as often proves to be the case when hypersensitiveness has been artificially produced by a previous serum treatment the desensitization program outlined may be shortened by starting with a slightly larger dose and increasing the size of the doses a little faster

One should always have on hand when attempting desensitization a syringe containing *epinephrine* ready for use Epinephrine is a specific for serum accidents Subcutaneous injection of 0 3 to 0 8 cc (5–12 minims) will usually prove effective in the milder accidents Injection should be repeated after a few minutes if necessary If the symptoms are alarming larger doses are indicated

George M Mackenzie

such as that from poison ivy which are easily dissolved in the fatty substances of the skin surface dyes which become fixed in the horny layer and come in close contact with the epidermis and local anesthetics such as procaine which have an affinity for epidermal structures Thousands of contactants have been identified as responsible for dermatitis They are associated for the most part with industry and trades The disease occurs frequently in bakers beauty parlor operators chemists exterminators furriers gardeners jewelers metal polishers munition workers nurses painters photographers printers tanners etc

Skin Responsiveness—Although quantitatively there is a wide variation in the capacity of the skin of different individuals to react no one is considered immune provided the epidermis is exposed sufficiently to repeated application of a known contactant The mechanism by which the skin becomes sensitized is wholly unknown No immune bodies have been discovered

Morbid Anatomy—The essential lesion is epidermal edema This occurs apparently as the result of an escape of fluid from dilated blood and lymph capillaries at the site of irritation As fluid continues to accumulate vesicles are formed within the epidermis and appear on the surface of the skin as small blisters In the more chronic stages prolonged rubbing may lead to hyperkeratosis and lichenification

Symptoms—The only symptom is pruritus felt as itching and burning at the site of the lesion In the acute cases there appears first an erythema with superimposed papules and then vesicles The time of appearance of the eruption following the initial contact is extremely variable Once hypersensitiveness is established however the lesion usually appears within twenty four hours after the last exposure In acute cases such as poison ivy itching may be felt within a few minutes in these cases scratching may convey the irritant to other parts of the skin In some instances where the process is very acute a generalized eruption may appear presumably from systemic absorption When there is continual contact as in certain industries the vesicular eruption is replaced by thickened fissured dry dermatitis Secondary infection is common

Differential Diagnosis—This concerns (*a*) the distinction from other types of eczema and (*b*) the detection of the specific contactant

Contact dermatitis may resemble the lesions of other types of eczema particularly atopic dermatitis which however is frequently associated with other atopic disorders as asthma and hay fever and this type of allergy is hereditary It occurs most frequently in infants and children and sites of predilection are the face neck and folds of the elbows and knees Contact dermatitis occurs most frequently in adults The distribution of the lesion frequently indicates the diagnosis and may even suggest the contactant at fault Thus an eczematous eruption limited to the skin about the eyes strongly suggests a cosmetic as mascara that which occurs only on the neck is frequently caused by fur dyes and that beneath the arms from dress shield material Other eczemas rarely have such a distribution

Detection of the offending contactant is made from the case history and from patch tests The site of the localized lesion suggests what the exposure might be and meticulous questioning will frequently elicit a clue The possible contactants are then applied to uninvolved skin Unlike intradermal tests the patch test material is gently rubbed onto the skin moistened if necessary covered with cellophane and held in place with adhesive material for twenty four to forty eight hours or less if intense itching occurs at the site of the test A positive reaction is an eczematous dermatitis at the patch site The contactant at fault will be revealed in about 40 per cent of the cases tested Precautions to be carefully observed are the removal of the patch if itching becomes marked and limitation of the number of tests at one time to twenty or less Necrosis of the skin and marked exacerbation of symptoms may occur if the application is too intense

Prognosis—All cases eventually recover sometimes quickly after the offending substance is removed

Treatment—It is a moot question whether the injection of extracts of at least some of the contactants will build up a resistance to them This is particularly important in poison ivy Although experimentally

appears after twenty four to thirty six hours There may be years between attacks or edematous areas may appear almost daily for years In rare cases there is a periodic *recurrence of attacks Involvement of the* genitals has caused urethral occlusion Visceral involvement much more common in the hereditary form may cause death by edema of the glottis Gastro intestinal crises with vomiting and abdominal pain have occurred in many familial cases Cases simu*lating acute ileus* ruptured tubal pregnancy appendicitis acute cholecystitis renal colic and intussusception are on record Kennedy has described cases of angioneurotic edema of the brain Fever may occur but from available reports leukocytosis seems to be rare

Associated skin lesions not infrequently observed are urticaria erythema multiforme, and purpura

Prognosis—In the hereditary form the danger of death from edema of the glottis is serious Of the 170 patients cited by Bulloch 21 1 per cent died in this way and 67 9 per cent of all the deaths were due to this lesion In the nonhereditary form the prognosis is much better Spontaneous cessation after a few months or a few years is to be expected Edema of the glottis is rare in this group

Treatment—Except in the small percentage of cases in which a specific allergy is found to be responsible for the occurrence of the swellings treatment accomplishes little or nothing In such patients elimination of the offending substance from the diet may prevent recurrences Osler s statement that 'treatment is very unsatisfactory is still valid Such nonspecific measures as administration of peptone *calcium lactate* or chloride or autogenous defibrinated blood and a variety of dietary restrictions have also been found ineffective Epinephrine and cold applications may be temporarily beneficial Ephedrine (0 025 to 0 05 Gm three times a day by mouth) has been found in some cases *to lessen the severity of* or even to abolish the symptoms tracheotomy may be required for edema of the larynx in the hereditary form A concurrent acute infection often causes a temporary disappearance of the swellings A therapeutic procedure which is sometimes effective is to restrict the diet *to one* or two simple foods such as rice and milk for ten days or two weeks The swellings may cease when the number of foods is thus limited If one article of food is then added at a time each three or four days after the previous addition, it may be possible to observe that when a certain food is given the swellings reappear and that when it is withdrawn the swellings disappear In some patients it is possible to discover by this method the offending food and to prevent recurrence of the swellings by its elimination from the diet Such treatment is however by no means always successful Histaminase is usually ineffective

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CONTACT DERMATITIS

Definition—Contact dermatitis is a common expression of allergy wherein an eczematous lesion of the skin appears after repeated contact with specific agents

Etiology—The two factors responsible *for the production of contact* dermatitis are (*a*) the nature of the offending agent (contactant) and (*b*) the responsiveness of the skin

Contactants—These vary from *simple* chemical substances to complex biological products Although strong chemicals applied to the skin may cause irritation the specific agents responsible for contact dermatitis are usually not irritating when first applied to normal skin Those which penetrate *the horny layer of the skin* most readily to reach the underlying epidermis are as a rule encountered most frequently Thus common contactants are plant oils

DISEASES DUE TO PHYSICAL AGENTS

AVIATION MEDICINE

Aviation medicine is that branch of medicine which deals with the health of the personnel engaged in the practice of flying civil and military aircraft. Owing to advances in the performance of the airplane at progressively higher altitudes and speeds the aviator has been exposed to hazards that *are characteristically different from those of* the worker and the military man on the ground. An understanding of the physiology of man under conditions of decreased barometric pressure is essential to the medical care of the aviator. As in industrial medicine generally preventive treatment assumes a predominant role.

The Selection of Aviators and Health Maintenance.—The selection of candidates for flying is one of the important duties of the flight surgeon. He must decide whether the man is fit to operate a plane in which not only his own health but that of passengers or the other members of the crew is involved. The physical examination is conducted with special care to determine the presence of those physical defects which would prevent the full efficiency of the aviator at altitude. This includes special consideration of the heart, eyes, ears, accessory sinuses and the central nervous system. The psychiatric examination is aimed to exclude the *unsafe* flyer, namely the psychoneurotic, the psychotic and unstable personalities. Special tests of physiological and mental functioning have been employed to determine the candidate's reaction to low barometric pressure; one procedure of this nature consists of observation of the impairment in emotional control which takes place as a result of altitude anoxia.

The maintenance of the health of airforce personnel, both the aviator and the ground crew, has become a complex problem. It must be steadily borne in mind that any illness, physical or mental, is not a personal problem but one that involves the lives of many others. Since the aviator may travel to all parts of the globe he is immunized with typhoid, tetanus and diphtheria vaccines and against other diseases to which he may be exposed or for which adequate vaccines are afforded. The seriousness of the venereal disease problem in civil and military aviation requires intelligent handling without the raising of a moral issue. Since *sulfadiazine therapy has demonstrated its* effectiveness in gonorrhea and its relative freedom from toxicity, this situation may now be dealt with in a far more favorable way than previously.

The employment of vitamins, especially A, C and the members of the B complex, may be of value in maintaining a high degree of fitness. In night flying it is evident that deficiency of vitamin A should be guarded against.

Use of military aircraft at temperatures which vary from minus 60° F in Canada and Alaska to 120° F in tropical countries has given the physician the responsibility of protecting the aviator against both undue heat and cold. With the spread of airplane travel after the war it is likely that many of the hazards which are now a daily occurrence in military aviation will be present to a varying degree in civil aviation.

Other threats to the health of the aviator include noise, vibration, aero embolism, air sickness, acute altitude sickness, fatigue states and the effects of acceleration such as blackout.

Acute Altitude Sickness.—Acute altitude sickness is a clinical disorder with characteristic symptomatology due to anoxia during high altitude flight. The term suggested by Schneider and used by Armstrong is adopted here since it distinguishes the condition from mountain sickness, which refers to the effect of continuous anoxia in mountainous regions. Since intermittent exposure to altitude anoxia in an airplane is not followed by acclimatization, it is important to treat this condition as a separate entity.

such prophylactic or phylactic treatment does not seem valid clinically there are many favorable reports The only certain cure is the discovery of the offending allergen and its avoidance

The principles of local treatment are important since drugs applied repeatedly to excoriated skin may cause a superimposed contact dermatitis on one for which treatment is sought Wet dressings of saturated solution of boric acid or 5 per cent aluminium acetate for the acute stage followed by a bland grease such as 3 per cent boric acid in nonallergic cold cream will often allay itching provided the contactant has been removed There is always danger of overtreatment and in severe stubborn cases hospitalization where the patient can be protected and nursed is recommended

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is below 85 per cent a rise in cardiac output takes place

Other effects of acute anoxia such as that on the adrenal gland the blood sugar and other blood constituents are now under intensive investigation

Symptoms—The symptoms of acute altitude sickness are characteristic varying with the degree of anoxia At an altitude of 12 000 feet there is in addition to the slight increase in breathing and elevation of the pulse rate a gradual onset of headache and lassitude especially if the exposure is longer than two or three hours An euphoric state manifested by overconfidence and undue hilarity takes place in about half the people exposed to anoxia in the others a depressed or sleepy tendency is noted At an altitude of 15 000 feet these symptoms are more pronounced and nausea and vertigo may develop At 18 000 feet about 25 per cent of normal individuals collapse in a period of one half to one hour Vomiting with severe headache may occur with more prolonged exposure to altitudes between 12 000 and 15 000 feet In certain persons the disturbance in mental function is completely unrecognized and unfortunately accompanied by such impairment in emotional control as to lead to seriously disturbed judgment The character of the mental disturbance is comparable to that produced by alcoholism As a result it has become difficult to convince pilots and others of the deleterious effect of altitude anoxia on the central nervous system and of the danger of flight while suffering from it

The effect of altitudes of 10 000 to 15 000 feet on the circulatory system is shown by an increase in pulse rate and a gradual though slight rise in systolic pressure The electrocardiogram reveals a characteristic depression in the height of the T wave When collapse takes place at an 18 000 foot altitude it is generally due to a peripheral circulatory failure characterized by a fall in blood pressure

Many tests of the special senses have been made to determine the effect of moderate anoxia on these functions By the use of angioscotometry an increase in the size of the blind spot has been conclusively demonstrated above a 10 000 foot altitude Dark adaptation and accommodative power are impaired at altitudes of 12 000 to 15 000 feet and above with decreasing visual acuity and light perception Neuromuscular control is diminished after exposure of one to two hours to altitudes of 12 000 and above Tactile sensation and hearing however are not generally affected until altitudes as high as 16 000 to 18 000 feet are reached

Prognosis—The effect of altitude anoxia such as is generally encountered in flight is temporary disappearing in a few hours or a few days depending upon the degree and length of exposure to oxygen want

Fatigue is one of the most common after effects of prolonged anoxia in aviators subjected to intermittent exposure to high altitude A fatigue state of a more chronic character sometimes takes place In most cases a long rest period is sufficient to overcome the condition In a few instances however a clinical disorder called 'aero neurosis by Armstrong develops as a result of the accumulative effects of repeated anoxia and the unusual hazards and responsibilities involved in flying This clinical entity is characterized by bodily and mental fatigue nervousness lassitude irritability and frequently by gastro intestinal disturbances

Treatment—Prevention of altitude anoxia seems the most rational approach to the treatment of this syndrome Since it has been adequately shown that oxygen want at moderate altitudes may produce sharp impairment in emotional control with a resultant potentially serious disturbance in judgment it is the responsibility of those in charge of civil and military aviation to use adequate oxygen inhalation for all members of the crew at altitudes above 10 000 feet and at lower altitudes in which prolonged flight takes place This point of view is additionally supported by the development in a limited number of aviators of chronic fatigue in which repeated exposure to anoxia may have been a factor

The oxygen apparatus employed has been in some instances a tube held within the mouth the so-called pipestem method Although it is effective at lower altitudes its disadvantage lies in the considerable variation in the concentration of oxygen inhaled and the ease with which the oxygen tube may be put aside Mask oxygen appa

Etiology—Swift ascent in an airplane to increased altitude brings the pilot and passengers to atmospheres in which the barometric pressure is progressively decreased This results in a lowered partial pressure of oxygen in the lungs with a consequent diminished pressure of oxygen in the arterial blood and in the tissues a condition called "acute anoxia'

Morbid Anatomy—Flight at moderate altitudes such as 5000 to 15 000 feet is followed by physiologic changes without demonstrable damage to the organs of the healthy individual This is also true of flight at altitudes between 35 000 and 44 000 feet when pure oxygen is breathed, leaving out of consideration the development of aero embolism The pathologic changes caused by severe oxygen want which may occur at very high altitudes on failure of the oxygen supply are those of asphyxia These consist of dilatation of the capillaries with increased

TABLF I

ALVEOLAR AND ARTERIAL pCO_2 AND pO AND ARTERIAL OXYGEN SATURATION OF SUBJECTS BREATHING AIR OR OXYGEN AT VARIOUS ALTITUDES

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permeability hemorrhage edema and perivascular infiltration Both small and large hemorrhages occur and affect the nerve cells in the cortex of the brain as well as the corpus striatum and medulla Hemorrhages also take place in the heart muscle mitral valve lungs kidneys and other organs

Pathologic Physiology—As the airplane ascends to increased altitude the most significant effect of the lowered barometric pressure is a progressive decrease in the partial pressure of oxygen in the lungs The inhalation of 100 per cent oxygen may compensate for the diminished alveolar oxygen pressure up to altitudes of 34 500 feet When an altitude of 42 000 feet is reached even during the inhalation of pure oxygen the oxygen saturation of the arterial blood is comparable to that found in a person without oxygen at an altitude of 14 500 feet (See Table I) The composition of air at these altitudes in terms of the concentration of oxygen carbon dioxide nitrogen, and the rare gases is the same but the pressure of oxygen in the lungs is characteristically lowered

Thus at an altitude of 12 000 feet the barometric pressure has fallen from 760 mm. to 483 mm of mercury The pressure of oxygen in the atmosphere may be calculated by multiplying 483 by 0 209 the percentage of oxygen in the air at any known altitude When the atmosphere is inhaled it is saturated in the lungs with water at a body temperature of 37° C resulting in a water vapor pressure of 47 mm of mercury The alveolar air in the lungs has a relatively constant pressure of carbon dioxide about 40 mm of mercury The actual pressure of oxygen on the capillaries of the lungs is therefore materially less than the fall in total barometric pressure would indicate which is a factor of considerable importance in calculating anoxia at high altitudes Thus, the alveolar oxygen pressure may be obtained through the following equation

$$[(483-47)\times 0\ 209]=40 \text{ or } 50 \text{ mm Hg}$$

instead of the sea level alveolar oxygen pressure of 108 mm Hg which may also be calculated by the above formula

This lowered pressure of oxygen in the lungs is insufficient to oxygenate completely the hemoglobin in the red corpuscles which results in an oxygen saturation of the arterial blood of approximately 85 per cent The tissues, which are thus in contact with a lowered oxygen tension respond with a varied symptomatology depending on the degree to which the various organs are impaired by anoxia The higher centers of the brain are most sensitive to oxygen want the heart next and perhaps the adrenal glands third but bone and muscle tissue are relatively much less affected

Stimulation of breathing is noticeable above 8000 feet and is more marked at 12 000 to 15 000 feet As a result of the increased volume of ventilation an increased proportion of carbon dioxide is eliminated from the lungs With the slight fall of carbon dioxide pressure there is a shift of the acid base equilibrium toward the alkaline side When an altitude is reached in which the oxygen saturation of the arterial blood

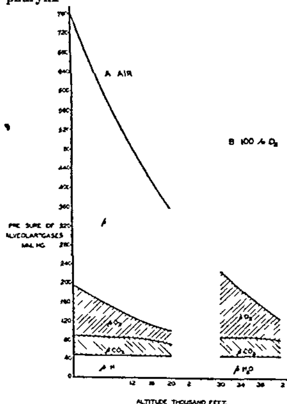
cury at pressures over 15 mm the discomfort is increased and frequently accompanied by tinnitus and actual pain The symptoms referable to the middle ear are more common as a cause of occupational disability and of passenger discomfort than all other complaints referable to air travel In some persons failure to obtain an equalized pressure on both sides of the drum may be followed by vertigo and deafness Inspection of the drum may reveal a moderate degree of redness

A chronic form of this condition takes place in which the ear drum is retracted and the drum membrane dull and thickened The patient complains of a full and stuffy feeling in his ears and of head noises Occasionally vertigo is present

Other effects of airplane travel on the ear are the noise and inevitable vibration which are more apt to affect the hearing than pressure changes in the middle ear

Treatment —Swallowing is the most common method of equalizing the pressure in the middle ear by opening the eustachian tube Chewing gum is helpful by creating a greater flow of saliva In many instances however the symptoms persist after swallowing It is then advisable to yawn repeatedly with the mouth as widely open as possible until the feeling of pressure disappears Sometimes it is necessary to hold the nose tightly and blow out with mouth closed in order to force air into the eustachian tube In rare instances if an equalization has not taken place and pain continues reascent to the higher level where pain first occurred and then gradual descent after pressure has become again equalized may afford relief The inhalation of helium-oxygen mixtures during or after descent may result in relief of pain since the smaller helium molecules may diffuse into the eustachian tube more readily than nitrogen Active treatment consists in inflating the tympanum by Politzer s method The instillation of copious quantities of water at a temperature of 110° F followed by dry heat is apt to relieve pain

Since pressure effects on the ears vary with the rate of ascent and descent the airplane companies have generally limited themselves to 300 feet per minute. Unforeseen conditions however may require that these rates be exceeded to ensure safety of the flight Both in military operations and in chamber experiments rates of ascent and descent of 3000 to 5000 feet per minute are generally well tolerated by persons who have no acute or chronic illness in the nose and pharynx



(A) Breathing air (B) Breathing 100% oxygen

Fig 46.—Fall in partial pressure of oxygen and carbon dioxide in the lungs at increasing altitudes A During ascent to an altitude of 20 000 feet there is a progressive fall in the pressure of nitrogen and oxygen in the alveolar air whereas the carbon dioxide pressure is only slightly lowered and the pressure of water vapor remains constant.

B Although 100% oxygen is breathed during ascent from 30 000 to 4 000 feet alveolar O is reduced to that which occurs in a subject breathing air at 14,500 feet The sum of water vapor and CO_2 pressure 83 mm Hg, constitutes at an altitude of 42 000 feet a far larger proportion of the total barometric pressure, 128 mm Hg than at the lower altitudes Thus the necessitous evolution of carbon dioxide and water vapor from the lungs limit more and more the quantity of oxygen that can be inhaled as progressively higher altitudes are reached

Aero embolism —Aero embolism is a clinical disorder due to formation of nitrogen bubbles in the blood and tissues of the body as a result of swift ascent to altitudes above 18 000 feet It is characterized by symptoms referable to the organ involved, most frequently by pains in the joints

ratus is more effective and may also be employed to administer 100 per cent oxygen Of these the *B L B mask is comfortable* and efficient employing a bag which allows a small amount of rebreathing and a sponge rubber disk which functions as a combined inspiratory and expiratory valve The Meter mask is equally comfortable and efficient but employs a collecting bag without rebreathing Delicate inspiratory and expiratory valves are responsible for minimal resistance in this mask an injector makes it possible to administer any oxygen concentration desired These masks operate on a constant flow of oxygen into the system which can be changed depending on the altitude reached The military services both here and abroad have devised special mask oxygen apparatus which function on a demand type of regulator in which a slight fall of pressure in the mask allows the entrance of sufficient oxygen for inspiration With the rise in pressure in the mask during expiration the inflow of oxygen is stopped at the regulator

There is no indication for the use of carbon dioxide in the treatment of altitude anoxia At low or moderate altitudes inhalation of oxygen enriched atmospheres prevents anoxia and its consequences such as hyperventilation and alkalosis At altitudes of 37 000 to 42 000 feet inhalation of pure oxygen is indicated since addition of carbon dioxide could only be made at the expense of a lowered oxygen pressure Due to the relative expansion of gases as the barometric pressure is lowered 2 per cent carbon dioxide at sea level would become over 15 per cent carbon dioxide at a 40 000 foot altitude Addition of this percentage of carbon dioxide would lower the oxygen in the inspired air from 100 per cent to 85 per cent evidence has been obtained that there is no value in replacing 10 per cent oxygen with 10 per cent carbon dioxide at these high altitudes

The actual treatment of persons previously exposed to altitude anoxia is return to a sea level atmosphere In patients who have been transported by airplane such as those suffering from cardiac or respiratory disease additional measures may be required The patient with coronary artery disease should not fly at altitudes of 10 000 feet or over without continuous inhalation of oxygen since there is evidence that this degree of anoxia may result in spasm of the coronary arteries and perhaps in thrombosis

Patients with pulmonary fibrosis and emphysema may suffer from serious dyspnea unless they inhale oxygen continuously when flying The physical expansion of gases at altitude may be responsible for distress in cases of therapeutic pneumothorax This applies also to patients with appendicitis or other lesions in the gastro intestinal tract in which expansion of the intestinal gas might result in perforation

Aero otitis Media —Aero otitis media is the term employed by Armstrong and Heim to describe acute and chronic traumatic inflammation in the middle ear caused by pressure differences in the tympanic cavity and that of the surrounding atmosphere As a result of similar changes of altitude in airplane flights, inflammation in the frontal and maxillary sinuses may also take place

Etiology —During ascent to high altitude the air in the eustachian tube is under increased pressure until the flapper like valve in the pharynx opens During descent a negative pressure exists in the eustachian tube until air has been admitted through its pharyngeal opening Inability to open the eustachian tube during changes in altitude may expose the middle ear to abnormally increased or decreased pressures and result in acute or chronic inflammation. In acute upper respiratory infection the opening into the eustachian tube or any of the accessory sinuses may be partially or completely closed by swelling of the mucous membrane Less disturbance is apt to be produced during ascent since the increased pressure of air in the eustachian tube and in the sinuses generally forces its way through even partially closed openings However during descent the flapper valve at the pharyngeal entrance to the eustachian tube may fold inward and effectually prevent the equalization of pressure Atmospheric pressure on the external surface of the middle ear becomes progressively greater than the pressure still existing on its inner surface If unrelieved hemorrhage and rupture of the drum may take place

Symptoms —A feeling of fulness in the middle ear is perceptible in most individuals at pressure changes of 3 to 5 mm of mer

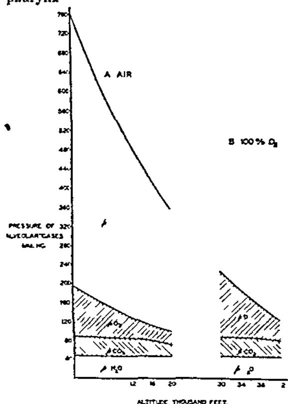
cury at pressures over 15 mm the discomfort is increased and frequently accompanied by tinnitus and actual pain The symptoms referable to the middle ear are more common as a cause of occupational disability and of passenger discomfort than all other complaints referable to air travel In some persons failure to obtain an equalized pressure on both sides of the drum may be followed by vertigo and deafness Inspection of the drum may reveal a moderate degree of redness

A chronic form of this condition takes place in which the ear drum is retracted and the drum membrane dull and thickened The patient complains of a full and stuffy feeling in his ears and of head noises Occasionally vertigo is present

Other effects of airplane travel on the ear are the noise and inevitable vibration which are more apt to affect the hearing than pressure changes in the middle ear

Treatment —Swallowing is the most common method of equalizing the pressure in the middle ear by opening the eustachian tube Chewing gum is helpful by creating a greater flow of saliva In many instances however the symptoms persist after swallowing It is then advisable to yawn repeatedly with the mouth as widely open as possible until the feeling of pressure disappears Sometimes it is necessary to hold the nose tightly and blow out with mouth closed in order to force air into the eustachian tube In rare instances if an equalization has not taken place and pain continues reascent to the higher level where pain first occurred and then gradual descent after pressure has become again equalized may afford relief The inhalation of helium-oxygen mixtures during or after descent may result in relief of pain since the smaller helium molecules may diffuse into the eustachian tube more readily than nitrogen Active treatment consists in inflating the tympanum by Politzer s method The instillation of copious quantities of water at a temperature of 110° F followed by dry heat is apt to relieve pain

Since pressure effects on the ears vary with the rate of ascent and descent the airplane companies have generally limited themselves to 300 feet per minute Unforeseen conditions however may require that these rates be exceeded to ensure safety of the flight. Both in military operations and in chamber experiments rates of ascent and descent of 3000 to 5000 feet per minute are generally well tolerated by persons who have no acute or chronic illness in the nose and pharynx



(A) Breathing air (B) Breathing 100% oxygen

Fig 46—Fall in partial pressure of oxygen and carbon dioxide in the lungs at increasing altitudes A During ascent to an altitude of 20 000 feet there is a progressive fall in the pressure of nitrogen and oxygen in the alveolar air whereas the carbon dioxide pressure is only slightly lowered and the pressure of water vapor remains constant.

B Although 100% oxygen is breathed during ascent from 30 000 to 42 000 feet alveolar O is reduced to that which occurs in a subject breathing air at 14,500 feet. The sum of water vapor and CO_2 pressure 83 mm Hg constitutes at an altitude of 42 000 feet a far larger proportion of the total barometric pressure 128 mm Hg than at the lower altitudes Thus the necessitous evolution of carbon dioxide and water vapor from the lungs limit more and more the quantity of oxygen that can be inhaled as progressively higher altitudes are reached

Aero embolism —Aero embolism is a clinical disorder due to formation of nitrogen bubbles in the blood and tissues of the body as a result of swift ascent to altitudes above 18 000 feet It is characterized by symptoms referable to the organ involved most frequently by pains in the joints

Etiology—The abrupt fall in atmospheric pressure which produces the elimination of free gases in the blood has been carefully studied in deep sea divers as caisson disease and by others at high altitude especially Armstrong who employed the term aero embolism to describe the condition All of the tissues of the body are saturated with nitrogen at sea level body fats dissolve six times as much nitrogen per unit mass as does the blood itself With rapidly decreasing atmospheric pressures gas bubbles may theoretically be formed at one half an atmosphere 18 000 feet altitude but are not common below 27 000 feet equivalent to one third an atmosphere The symptoms of aero embolism are apt to take place in most subjects unless special means of prevention are undertaken

Pathological Physiology—At sea level pressure 100 cc of blood dissolves 1.5 cc nitrogen 0 25 cc oxygen and 0 83 cc carbon dioxide although larger amounts of oxygen and carbon dioxide are carried in loose chemical combination The pressure of carbon dioxide in the body is governed by the alveolar carbon dioxide pressure which is an approximately constant pressure of 40 mm of mercury in the healthy state The oxygen pressure in the tissues even during the inhalation of 100 per cent oxygen at sea level never rises to high levels since 5 to 6 cc of oxygen in 100 cc of blood are consumed by the tissues The oxygen pressure in venous return blood is probably therefore, never higher than 50 mm of mercury However nitrogen is physiologically inert and goes into simple solution in the body fluids in an amount dependent on the partial pressure of nitrogen in the lungs When the airplane makes a swift ascent to a high altitude such as 40 000 feet nitrogen at a former sea level pressure of 560 mm of mercury in the body fluids is abruptly in contact with an atmosphere in which the total pressure is 141 mm and the blood nitrogen pressure almost zero

This excessive pressure differential is responsible for the evolution of nitrogen bubbles The sea level pressure of oxygen and carbon dioxide are not sufficient to cause bubble formation but after a nitrogen bubble has been formed oxygen and carbon dioxide diffuse into it according to their relative partial pressures

Symptoms—The symptoms depend on the number, size, and location of the bubbles The most frequent complaint is pain around one or more of the joints which represent an embolus in the bone periosteum or tendinous connections about the joint At first it feels like an ache but swiftly grows worse and in fifteen minutes may become intolerable Other frequent symptoms are itching in the skin with at times urticarial lesions In about 6 per cent of the cases the lungs are the cause of severe symptoms Gas emboli picked up from the tissues by the venous blood end in the pulmonary arterioles and capillaries The patient complains of burning pain followed by prolonged coughing spells Edema of the lungs develops quickly and descent to sea level is necessary to get rid of the edematous fluid in the alveoli by effective coughing

The most serious location for embolism is the central nervous system A few cases of such involvement have been described in which paralysis unconsciousness and convulsions occurred In all these instances there was prompt recovery without any permanent after effects after the subjects were brought to sea level pressure Although increase in spinal fluid pressure has been reported recent investigations have indicated that the pressure in the spinal fluid is not definitely affected by lowering of the barometric pressure

Treatment—Prevention of aero embolism should be carried out whenever possible In commercial flying an altitude of 18 000 feet should not be exceeded unless a sealed pressure cabin is used On military missions when higher altitudes are necessary several procedures are employed Since it has been known that certain individuals are less apt to develop aero embolism than others preliminary tests in a low pressure chamber are utilized to select those aviators who are less likely to develop the condition

A more reliable method is to allow the aviator to inhale pure oxygen for a period of one to three hours before ascent to high altitude The inhalation of oxygen results in a progressive diffusion of nitrogen through the lungs In five hours approximately 95 per cent of the dissolved nitrogen is elim

inated from the body Exercise both active and passive, increases the cardiac output and the elimination of nitrogen

Since there is no reliable method of knowing whether a man will consistently be free of aero embolism at altitudes above 30 000 feet nitrogen desaturation by inhalation of pure oxygen should be used wherever possible for a period of two or preferably three hours This is especially important in airplanes where large crews are operating in which development of the symptoms in one member may necessitate abandonment of the mission Although aero embolism is confined to the military air services it must be remembered that sealed cabin planes were already operating in commercial transports before the war It is very probable that pressure cabin flying will undergo a swift development after the war because of greater speed and comfort in traveling At altitudes above 20 000 feet a leak in the pressure cabin with sudden fall in pressure may cause symptoms of aero embolism in some of the passengers

Effect of Accelerations on the Body — The effect of acceleration on the body is most commonly seen in the so called 'black out' in which a flyer pulls out from a dive and for one to three seconds is unable to see This sudden loss of vision takes place also if a turn is made at high speed

Speed itself has no effect on the human body if it is constant in rate and direction provided the individual is protected against the blast of the wind Acceleration which may be defined as the rate of change of velocity produces sudden and profound effects on the body The military forces are intensively concerned with measures which will prevent harmful effects of acceleration and with procedures which may allow the aviator to withstand higher accelerations without blacking out both in dive bombing and in swift turns at high altitude fighting

Acceleration or a change in the velocity of the body may take place theoretically if the airplane is moving in a constant direction and the speed is suddenly either increased or decreased as for example when the brakes of the airplane are suddenly applied The second and almost the only form in which acceleration is actually produced in flight is for the speed to remain relatively constant and for the direction to suddenly change thereby subjecting the body to an abnormal force The amount of force developed in accelerations which are simply due to change in speed called *linear accelerations* are calculated from Newton's law $F = MA$ in which the force is proportional to the mass and the acceleration When the acceleration is created by a change in direction that is by centrifugal acceleration, the amount of force is calculated from the equation $F = \frac{MV_2}{r}$ in which V = velocity r the radius of the turn and M the mass

The pull of gravity which attracts us to the earth has been selected as the unit to measure the force exerted on the body during acceleration in flight This can be expressed in terms of the body's weight since it is proportional to mass In aviation medicine the symbol 'g' is employed to report the force which attracts us to the earth, thus 2 gs is twice that force and 5 gs five times that force

Although there is no difference between the effect of acceleration forces which arise from linear or centrifugal acceleration the axis of the body through which the force acts is important When the pilot is seated in the conventional manner in aircraft and pulls out from a dive or turns at a high velocity a force is exerted directly through the long axis of the body from head to foot and is termed *positive* acceleration Both the duration and the magnitude of positive acceleration determine the *degree of black out* It has been found that 7 gs cannot be maintained for more than three seconds in a pull up from a dive or 4 gs for more than five seconds

The principal effect of a force of 2 gs acting on the body is a feeling of increased weight in the limbs This is increased to a sensation of being pressed down into the seat at 3 gs and at 5 gs there is also clouding of vision as though a gray veil were in front of the eyes In the average person 5 to 6 gs will cause the symptom known as blackout a temporary loss of vision At this time the body is markedly compressed in a vertical position and the head feels as though it were being pressed into the shoulders Above 6 gs consciousness is lost if the acceleration lasts two seconds Considerable variation exists

in the extent to which acceleration can be borne, depending upon the time and on the type of individual Tall, slender men are less resistant to centrifugal force than small heavy set people and persons with high blood pressure do better than those with low blood pressure

The mechanism of blackout can be traced to the effect of high centrifugal force on the blood stream A force acting in the direction of head to foot tends to prevent blood from flowing from the foot to the head The venous return of blood to the heart is decreased and there is a force which tends to retard the flow of blood toward the head in the arterial system Added to that there is undoubtedly a sudden cessation of the flow of blood in the capillaries When the arterial blood supply to the eye falls below a certain level vision fails and soon after that the brain becomes inadequately supplied with blood and consciousness is lost The fundamental effect is that of acute anoxia which is especially harmful to the organ most sensitive to oxygen want, namely, the central nervous system

Treatment—The treatment of this condition is in the first place to select aviators who tolerate it better than others If it were possible for the crew to be placed prone in the airplane the acceleration forces set up in dive bombing would act transversely across the body without causing blackout or with a marked diminution in its severity This has not so far been found practical An inflatable abdominal belt has been found helpful though not comfortable The most practical method of reducing the effects of centrifugal force is sitting in the forward crouch position in which the trunk is tilted forward and the knees drawn upward This position decreases the distance which the blood has to be pumped vertically and the large blood vessels of the trunk are not in the direct line of acceleration It has been found that a person may tolerate an additional 2 gs if he adopts the forward crouch position

ALVAN L BARACH

SEA SICKNESS AND AIR SICKNESS

These two conditions are in all probability due to the same causes and can be considered together Air sickness and sea sickness may be defined as conditions due to frequently repeated oscillatory movements of the body in a ship or airplane, and characterized by dizziness, nausea vomiting pallor and sweating

Etiology—In a ship the pitching seesaw movement on a transverse axis through the center of the ship the rolling movement on its long axis the movement of the entire ship up and down and the vibration occurring in most ships constitute the usual motions to which an individual is subjected In airplane travel there are vertical accelerations excessive rotary motions and vibration which bring on the disturbance Although many possible mechanisms have been described for both these conditions all the available evidence favors the belief that motion sickness is essentially due to disturbed vestibular function It is also true that visual psychogenic, and kinesthetic factors play a subsidiary role varying with the individual

Symptoms—The symptoms may come on without warning A man who was previously in good spirits may suddenly become quiet and subdued He feels nauseated and is aware of excessive salivation Mental depression is almost constantly present Vomiting may then take place with mild headache Pallor and cold sweats are common, true vertigo is rare There are no characteristic objective signs although a drop in systolic blood pressure has been reported accompanied by tachycardia or a slow pulse rate The nervous component in both air and sea sickness is at times important Some individuals will develop the condition after the briefest possible exposure It is sometimes brought on by bad odors or poor ventilation

Treatment—Fixing the eye on a definite object in space undoubtedly is of real help in both air sickness and sea sickness The eye should not be allowed to shift with the position of the airplane as the earth or sky will swim past the eyes and produce dizziness or nausea in a manner comparable to the development of this condition when one whirls rapidly on a piano stool The eye should remain fixed on an object on the ground or on the horizon

Abdominal belts and supports have been found helpful by many investigators by

reducing the movement of the heavy viscera or perhaps by preventing venous pressure changes in the abdominal veins If it is possible to lie supine in the center of the airplane or ship less disturbance is apt to be felt Many drugs have been advocated which either act as sedatives to the entire organism or effectively suppress the parasympathetic nervous system The combination of belladonna and a sedative drug has much to support it In the latter category sodium amytal and phenobarbital are most highly thought of Any drug which would cause dilatation of the pupils or reduce efficiency by sedation would be questioned by the military forces However the use of moderate doses of these drugs might be preferable even in combat to the incapacity which severe motion sickness induces

In sea sickness the judicious and even injudicious use of alcohol has been given a high place as a therapeutic agent both by professional and lay observers

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COMPRESSED AIR ILLNESS

(Caisson Disease The Bends Divers Palsy)

Compressed air illness is produced in individuals who after having breathed air under a pressure of considerably more than 1 atmosphere are subjected to unduly rapid reduction of air pressure The disease was described in 1841 by Triger a French engineer who first employed a caisson in 1839 With the great increase in the use of compressed air in deep water diving and in such engineering operations as pier construction and tunneling numerous opportunities for the development of the malady occur

Etiology —Workers entering a caisson pass through an airlock or chamber where the pressure is elevated to that of the working space On leaving the caisson decompression is also effected in the airlock If the change takes place too rapidly the atmospheric nitrogen dissolved in the body under pressure is liberated as nitrogen bubbles which when sufficiently profuse obstruct the circulation It has been assumed that these bubbles in nerve tissue fat tendon sheaths fascia intestinal mucosa and throughout the body give rise to caisson disease However recent studies conducted by Behnke and his associates indicate that gas bubbles to which symptoms could be attributed were observed only in blood vessels and it is believed by these investigators that the etiology of bends is essentially the result of embolic ischemia of osseous tissue

There is little or no danger in rapid decompression from working pressures of 15 pounds* or less. At pressures above this however caution must be exercised to avoid overexposure of workers and unduly rapid decompression. Although various methods and rates of decompression have been proposed no one schedule at the present time is universally used. Rules and regulations governing work in compressed air have been adopted by the U S Navy Department and by legislation in some states. The uniform method of decompression is favored in some regulations and the interrupted or stage method in others. The relative merits of the two methods remain to be determined.

The use of oxygen instead of air during the later stages of decompression has been demonstrated as effective in materially reducing the time of decompression.

Experimental work with respirable mixtures of helium and oxygen used as substitutes for normal air has shown that helium is about half as soluble as nitrogen in body tissues is more rapidly diffused, and that the use of helium oxygen mixtures permits of more rapid decompression than is possible after exposure to compressed air.

Cases of collapse have occurred in submarine escape training with the Momsen lung used in the United States Navy. Most have developed in ascents from depths of less than 5 fathoms (equivalent to less than 15 pounds gauge pressure) and cannot be attributed to caisson disease. Polak and Adams have recently ascribed the cause of collapse or death in these cases to air embolism.

Symptoms—The more important evidences of compressed air illness in order of frequency are (1) localized pain in one or more extremities or in the abdomen ("the bends") which is the only symptom in about 90 per cent of the cases (2) vertigo ("staggers") which occurs alone or with other symptoms (3) involvement of the central nervous system monoplegia or diplegia due to cerebral irritation or sensory and motor disturbances attributable to the presence of gas bubbles in the spinal cord (4) cutaneous manifestations ("itch") (5) asphyxia ("the chokes") and (6) collapse and unconsciousness. Characteristic bone changes appearing in caisson workers have been demonstrated by x ray examination. The onset of symptoms in about 50 per cent of the cases occurs within thirty minutes after decompression in 90 to 95 per cent within three hours.

Prognosis—If promptly and properly treated the chances of complete recovery are excellent. Cases untreated for several hours after the onset of symptoms are not so favored. Recovery after collapse is doubtful.

Compression Effects—During rapid compression violent pain in the ear ("ear block"), and even rupture of the tympanum may occur because of difference in pressure on the two sides of the tympanic membrane. Similarly air under pressure may become trapped in the sinus ("sinus block") causing acute pain. Infections of the upper respiratory passages may partially obstruct the aural and sinal spaces and thus cause a difference in pressure between adjacent spaces resulting in congestion edema and hemorrhage. Impaired hearing vertigo and autophony may be caused by hemorrhage into the middle ear and vestibule.

Other compression effects result from the constituent gases of the air. At high pressures oxygen may cause convulsive seizures which may attack the worker with little warning. Nitrogen absorbed under high pressure exerts a narcotic effect on the subject and impairs his ability to perform mental tasks. The effect can be minimized or abolished by the substitution of helium for nitrogen. The partial pressure of carbon dioxide at a depth of 200 feet rises to about 7 per cent of an atmosphere. Such a high concentration may cause unconsciousness in some workers after a short exposure.

Treatment—Treatment of caisson disease is essentially recompression and subsequent slow decompression. No standardized method has been adopted. A procedure recently recommended is to place the subject at the earliest possible moment after the onset of symptoms in a steel chamber or "medical lock" where pressure is applied until all symptoms are relieved and in addition to add 1 more atmosphere in the effort to completely restore blood supply to the affected tissues. The patient is subjected

* A working or gauge pressure of 15 pounds represents pressure above that of a single atmosphere

to this pressure for a minimum of thirty minutes, then the pressure is reduced to 30 pound gauge and oxygen is substituted for air which the patient breathes for one and a half hours during which period the return to normal pressure proceeds Unrelieved symptoms require a prolonged stay (overnight soak) at a pressure of 30 pounds or under for a period of twelve to twenty four hours followed by a gradual decompression to atmospheric pressure

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MOUNTAIN SICKNESS

The ascent to high altitudes of persons accustomed to life under the pressure of practically one atmosphere (760 mm mercury) may produce distressing and possibly serious consequences The effects of diminished pressure may be manifested quickly if the ascent be rapid as in aeroplanes or balloons or more gradually during mountain climbing These are produced not by the reduction of mechanical pressure but result from the diminished partial pressure of oxygen In individuals permanently resident in rarefied air there are structural and functional adaptive changes Few persons escape slight discomfort at least on ascending more than 12 000 feet above sea level

The principal factors in acclimatization are (a) increased volume of air breathed (b) increased alveolar oxygen pressure (c) increase in red cells in proportion to the increase in hemoglobin (d) increase in size of red cells (e) increase in viscosity of the blood and in resistance to hemolysis (f) increase in serum proteins (g) diminution in available alkali (h) decreased alveolar carbon dioxide (i) decrease in arterial oxygen saturation At high altitudes new formation of red cells has been indicated by the large percentage of reticulated cells in the blood Hurtado found an increase in the mid capacity of the lungs a true physiologic emphysema and augmented vital capacity

Symptoms of mountain sickness differ in kind and severity in different individuals and at different altitudes In mountain climbing the effects of diminished pressure may be observed at much lower altitudes than in aviation because of the association of rarefied air and more or less severe physical exertion Individuals suffering from cardiovascular disease are of course at a peculiar disadvantage and in them the effects of a rarefied atmosphere are correspondingly intensified Frontal headache vertigo malaise mental dulness abnormalities of vision and hearing epistaxis nausea vomiting thirst cyanosis dyspnea palpitation and muscular weakness are commonly noted There may be slight fever The pulse is accelerated and the systolic blood pressure moderately raised With rest some degree of accommodation is ordinarily acquired within a few days Oxygen affords prompt relief

The effects upon aviators of rapid ascent and descent are of a somewhat different character Few symptoms are noted on ascending short of 12 000 feet Dyspnea is then common and as the altitude is increased headache muscular weakness apathy and psychic disorders may be manifested At an altitude of 20 000 feet fliers are in danger of collapse without oxygen supply With oxygen equipment they can climb to 40 000 feet without serious effects but at altitudes much beyond this symptoms of anoxia must be expected even when pure oxygen is breathed

Aside from the effects of low barometric pressure flying personnel engaged in military operations encounter many additional hazards Important among these are aero embolism ("altitude bends") a condition analogous to compressed air illness effects of vibration noise and of speed the most dangerous of which is transient blindness (blacking out) and unconsciousness resulting from sudden change of direction severe stresses and strains from low temperatures effects of pressure variations in the auditory canals and paranasal sinus passages, pilot fatigue and psychological tension and loss of sleep

Treatment —To relieve oxygen want in mountain sickness, oxygen should be given Discussions on methods of protection of flying personnel against the many hazards that are encountered and the treatment of affections following exposure to these hazards can be found in the chapter on aviation medicine (p 495)

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HEAT EXHAUSTION AND HEAT STROKE

Exposure to high heat particularly when it is associated with high humidity may result in quite diverse effects varying from the superficial manifestations of radiant heat to heat cramps heat exhaustion heat stroke (heat hyperpyrexia thermic fever), or sudden death

Heat exhaustion is characterized by pronounced weakness dizziness stupor pallor profuse perspiration diminution of urine, acceleration of the pulse rate and of respiration, and a lowering of blood pressure. There is rarely loss of consciousness Occasionally cramping pain in the muscles of the abdomen or extremities may be noted The mouth temperature may be subnormal or slightly elevated Morton with an extensive tropical experience states that the rectal temperature is invariably raised, usually to 101° F The apparent onset is usually sudden and not necessarily associated with exertion Under conditions of sustained heat, as in the tropics there may be during several days prodromal headache anorexia constipation and muscular weakness The death rate from heat in the United States according to Shattuck who collected records for a thirty three year period (1900-1932) amounted to 0 39 per 100 000 He found that deaths from heat closely correlated with unusually high atmospheric temperatures continuing for several days and are far more common in men than in women Air conditioning particularly dehumidification and cooling during the hot months offers a practical means applicable in many instances of mitigating the heat hazard indoors

In heat stroke or sunstroke the heat regulating mechanism of the body is seemingly overwhelmed and not merely embarrassed as in heat exhaustion In typical cases heat exhaustion and heat stroke are readily differentiated but there is no clear line of demarcation between the two conditions and cases of heat exhaustion may develop evidences of heat stroke The onset of heat stroke may occur with catastrophic suddenness and death be almost instantaneous or there may be premonitory headache dizziness nausea or visual disturbance Consciousness is lost early in the attack The face is flushed the skin dry and hot The temperature is elevated in the more severe cases to 109° F or more In the early stages of heat stroke the pulse is full and rapid, the breathing deep and the pupils possibly dilated As the patient's condition becomes progressively worse the pulse grows irregular rapid and more feeble the breathing more shallow and of the Cheyne-Stokes type Death may occur within a few minutes but if the patient survives the second day, re-

covery is probable Persistent susceptibility to heat and impairment of memory are commonly noted after severe attacks of heat exhaustion and heat stroke Hemiplegia and paraplegias are not uncommon sequels Signs of a damaged myocardium in the electrocardiogram immediately after heat stroke have been reported by Metz who recommends that in every case an electrocardiogram especially with functional trial should be made The predominant pathologic manifestation in the brain is edema followed by petechial hemorrhages A rather extensive hemorrhage under the endocardium of the left ventricle was noted in four fatal cases examined by Wilson who believes this to be probably the actual cause of death

Morton found in cases of heat stroke an increase of blood lactic acid and a lowering of plasma CO_2 After twenty-four hours the blood urea was markedly increased and blood and urinary chlorides reduced Hall and Wakefield observed in dogs which had reacted with the clinical picture of heat exhaustion or heat stroke renal damage with high nonprotein nitrogen a marked decrease in the alkali reserve in all cases very high blood lactic acid commonly an increase in blood chlorides and the blood sugar and total nitrogen not notably changed The serum *p*H was decreased in all cases and in organic phosphorus and serum calcium slightly increased

Heat cramps occurring in persons exposed to high heat studied in 1892 by Cronin and others have in recent years occasioned many investigations and reports The condition is found particularly among stokers miners steelworkers and others subject to intense heat and profuse perspiration The onset is usually sudden Spasms involve successively groups of muscles of the extremities or of the abdominal wall and may occur intermittently for twenty four hours seldom longer Heat cramps are now attributed to dehydration and the loss of blood chlorides This loss may amount to 20 Gm or more daily The intake of large quantities of water results in the muscular spasms a circumstance probably related to diffusion effects It is wholly possible that in some cases the cramps are due to the retention in the blood of toxic elements particularly in view of the prompt beneficial effects of the intravenous injection of sodium bicarbonate

Treatment *of heat exhaustion* usually calls only for rest in a cool place Purgation may be indicated In severe cases stimulation may be required to offset the depression and cooling sponges or warm baths to favor return of the temperature to normal Morton advocates 1 drachm of glucose and 15 grains of sodium bicarbonate to 1 ounce of water hourly for twenty four hours and in severe cases particularly those with muscular spasm 1 to 1½ pints of 2 per cent sodium bicarbonate solution intravenously

Heat stroke demands prompt and often heroic treatment Icewater baths cold sprays ice packs and ice-water enemata may be used until the temperature is reduced to about 102° F cold sponges may then be employed The heart should be carefully watched and if evidence of pulmonary congestion appears venesection should be performed

Heat cramps may be prevented in large measure by supplying men exposed to high heat with salinized water (0 1 per cent sodium chloride solution cooled to about 50° F) Salt tablets are now commonly dispensed in industrial establishments presenting high heat hazards and though not as desirable are more convenient than salt solutions Cases of heat cramps may be treated with saline fluids rest and warm baths Sedatives may be helpful It is likely that the use of salinized fluids would be of value in preventing many of the effects of heat exhaustion among those exposed to continued high temperatures

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ELECTRIC SHOCK

Electric shock may result when the body becomes part of the path of flow of current between poles of different potential Broadly speaking alternating currents are considered much more dangerous than direct currents With direct current the flow is in a single direction, with alternating current the direction is frequently reversed the frequency being expressed as cycles per second Fatal shock seldom results from contact with a direct current of less than 300 volts but the danger increases as higher voltages are attained Alternating currents if of few cycles (15 to 60) may cause death in well grounded subjects even at the 110 to 115 volts commonly used for home lighting but alternating currents of high voltage if of very high frequency may be handled with relative safety Maclachlan concluded from an analysis of 479 cases of electric shock that the severity of shock decreased or the success of resuscitative efforts increased as the potential of the circuit involved increased The resistance offered by the body as a conductor is a factor in determining the severity of shock The intensity of a current is measured by dividing its tension or voltage by the resistance in ohms the result being expressed in amperes The resistance of dry skin is about 50 000 ohms per square centimeter, varying in different parts of the body Moisture from sweating or wet clothing may lower the resistance to 1200 or 1500 ohms If skin resistance reaches 1200 ohms an alternating current of 110 volts may prove fatal The nature of the 'ground may determine the seriousness of shock A subject immersed in a water filled bath might be killed by a current which could be tolerated under other circumstances The duration of contact is also of great importance as the severity of shock increases with an increase in the duration of contact Prolonged contact with low voltages is more likely than with high voltages as in the latter case the victim very often falls clear aided by violent muscular contractions

Etiology —The tendency of currents of low voltage is to arrest the heart without affecting the respiration Alternating currents of low tension throw the heart in fibrillation High tension currents affect the central nervous system causing inhibition of respiration In one the result is heart death, and in the other respiratory paralysis It is inadvisable to generalize regarding the action of currents of moderate tension as many variable factors such as skin resistance grounding source voltage amperage duration of contact and kind of current determine the severity of the shock Much remains unknown concerning the mechanism and the effects of electric shock, although the studies of Urquhart Nahum and Hoff Maclachlan, Wills and their associates have contributed greatly to knowledge in this field

Morbid Anatomy —Postmortem evidences of electrocution are variable Extensive charring may mark the points of entrance and exit of the current or the burns may be slight or absent The superficial destructive effects of direct currents are usually more extensive than those of alternating currents The blood is often dark and is rarely coagulated Minute hemorrhages and areas of destruction may be found in the brain and cord Reference should be made to the detailed reports of studies of the effects of electric shock upon the nervous system published by Langworthy and Kouwenhoven and Morrison Weeks and Cobb

Symptoms —Loss of consciousness momentary or prolonged and burns of varying degree usually accompany severe electric shock Death may be instantaneous or result after some moments or hours Convulsions and priapism are common Those who recover from shock may suffer various after effects such as persistent muscular pain fatigue headache and nervous irritability Progressive loss of vision with opacity of the lens has been reported There are usually no permanent effects in those recovering from shock Because of the tendency to electrolysis of deep tissues and to the destruction of vessel walls the possibility of delayed hemorrhage must be kept in mind in the treatment of cases involving extensive burns

Prognosis —In cases of cardiac failure due to ventricular fibrillation death must be expected Respiratory paralysis often responds to artificial respiration (In experimental animals however cardiac function has been restored after induced ventricular fibrillation Hooker Wiggers) Jex Blake considered death due to (1) prolonged muscular tetany resulting in asphyxia, (2) ventricular fib-

rillation (3) respiratory failure through effects on the nervous system or (4) delayed effects of burns To these causes Langworthy and Kouwenhoven would add the more immediate effects of heat production and tissue coagulation

Treatment —When the victim is freed from the current artificial respiration is the measure first necessary in the treatment of electric shock It should be instituted at once as a delay of even moments may result in death Numerous official bodies concerned with electric shock have recommended the prone-pressure method which should be continued until rigor mortis sets in One case at least has been revived after eight hours of effort There is some evidence that the return of normal respiration is hastened by the supplementary use of oxygen or oxygen carbon dioxide inhalations Counter shock or stimulation by mechanical means has been advocated but there is little or no reason to believe that it is of value Different authors following the experimental work of Levy who showed that ventricular arrhythmias leading to ventricular fibrillation and death could be induced by conditions which stimulated the heart and by equivalent conditions which removed or reduced depressing influences have called attention to the often fatal consequences of administering adrenalin and other stimulating drugs in electric shock Nahum and Hoff discovered that acetyl choline given to experimental animals protects them from ventricular fibrillation and death when they receive an electric shock of the strength which normally causes fibrillation of the ventricles The important clinical application which is suggested by these findings is obvious Spinal punctures as a hospital procedure in the after treatment for persistent headache or signs of cerebral pressure are of some value

W J McConnell

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DISEASES DUE TO CHEMICAL AGENTS

CARBON MONOXIDE POISONING

CARBON monoxide is a gas produced by the imperfect oxidation of carboniferous material and is probably the most widely distributed of toxic agents It is colorless, in ordinary concentrations odorless, and is slightly lighter than air Ordinarily carbon monoxide does not appear in nature, but results almost entirely from the incomplete combustion of material containing carbon It may be encountered in the home through accidental leakage of manufactured gas from open burners and defective appliances and from incomplete combustion of various commercial gas products and in many industries particularly in coal mining in the steel industry *in processes utilizing gas heat and* in connection with the use of explosives in confined spaces It is found in smoke in compartments which have been painted with oil paints and sealed and in the exhaust of internal combustion engines Many deaths have occurred in closed garages from motor exhaust gas and manufactured gas long has been employed in suicide Coal gas contains about 16 per cent carbon monoxide blast furnace stack gas 28 per cent mine air after dust explosions 1 to 8 per cent and the exhaust from automobile motors about 7 per cent

Incidence —Without doubt countless persons are daily affected to some degree by carbon monoxide There is a striking variation in individual susceptibility but no evident racial or sex predisposition Children are believed to be more susceptible than adults probably because of their relatively greater respiratory exchange body weight considered Individuals with cardiorespiratory disease are handicapped when exposed to CO and the preexistence of certain nervous disorders may in persons poisoned result in aggravation of the nervous manifestations Some degree of acclimatization to carbon monoxide develops among those continually or frequently exposed to the gas and is shown in the lessening of symptoms during successive exposures to the same concentrations The possible explanation of this acclimatization is suggested by Killick as due to (1) a selective activity of the alveolar membrane producing either a secretion of oxygen from the alveoli into the blood, or an excretion of carbon monoxide from the blood into the alveoli, or (2) removal of carbon monoxide from the blood by oxidative or other processes in the tissues

Etiology —Carbon monoxide has an af*finity for hemoglobin two hundred to* three hundred times that of oxygen The reaction however, is reversible and depends upon the relative tensions of CO and O_2 in the alveolar air The gas is harmful in that it produces *anoxemia Death is due to respira*tory failure Though the problem has occasioned much study it has not been demonstrated that CO is of itself, specifically toxic Haldane has suggested that it may poison a catalyst of oxidation

Poisoning depends not only upon the CO content of inspired air but also upon the duration of exposure to the gas Particularly when exposed to moderate concentrations the blood does not attain *the full* saturation theoretically possible The maximum allowable concentration of carbon monoxide recommended by the American Standards Association is 100 parts per 1 000 000 parts of air by volume with atmospheric oxygen not below 19 per cent by volume for exposures not exceeding a total of eight hours daily and 400 parts per 1 000 000 parts of air by volume for exposures not exceeding a total of one hour daily

Morbid Anatomy —In the postmortem examination of victims of CO poisoning there is often noted a bright, cherry color of the blood Lining membranes are exceptionally red or show ecchymoses *Particu*larly important are pathologic changes in the brain characterized by hyperemia edema hemorrhage and diffuse degeneration Softening in the lenticular nucleus is regarded as the most typical *lesion in* CO

poisoning Chornyak and Sayers found in dogs that the cells of the cortex the corpus striatum the dorsal motor nucleus of the vagus and the dorsal sensory areas of the medulla were especially involved Neurons were severely damaged showing disruption marked chromatolysis and other degenerative effects Though still a matter of some dispute the effects of CO upon the nervous system are generally considered to be due essentially to asphyxia and not to immediate toxic action There have been reports of the disappearance of chromatin from adrenal capsules and of colloidal material *from the thyroid in cases of acute poisoning*

Symptoms.—Sayers and Yant observed that the character and severity of symptoms under any degree of blood saturation depended largely upon the duration of exposure and the accompanying muscular activity and further that with a blood concentration resulting from long exposure to a low atmospheric concentration there were noted more severe symptoms and after-effects than with a similar blood concentration resulting from a short exposure to a richer CO mixture In general a concentration of 0 06 per cent or 6 parts of carbon monoxide in 10 000 parts of air produces headache within an hour and unconsciousness in two hours while 0 1 per cent carbon monoxide or 10 parts in 10 000 produces unconsciousness in a little more than an hour and may prove fatal in four hours

Carbon monoxide may kill with great suddenness Victims of mine dust explosions have been found in attitudes indicating that there was no warning of impending danger Though headache is usually the first symptom the onset may be insidious There have been many cases displaying a progressive muscular weakness without loss of consciousness but with disturbances of memory the victim passing into a rather insouciant oblivion from which he may emerge quite promptly or from which he may pass into full coma

The after effects in those recovering from acute poisoning are extremely varied Headache vertigo muscular weakness and nausea are common More rarely encountered are serious disturbances of memory vision hearing and speech or psychoses neuritis and paralyses Cerebral hemorrhage has been observed some days after apparent recovery Pneumonia quite often ensues and a great proportion of hospital patients with CO poisoning have fever and a marked leukocytosis

Chronic poisoning by CO is believed by many authors to be a clinical entity It is certainly true that in many individuals repeatedly long exposed to small amounts of CO there are such evidences of disease as persistent headache malaise and an ill defined debility

Diagnosis.—Absolute diagnosis is dependent upon the identification of carbon monoxide hemoglobin The *pyrotannic acid* method affords a reasonably accurate quantitative estimation of CO in blood or air Of the laboratory methods the iodine pentoxide method though time-consuming is now the generally accepted standard of accuracy for CO analysis Carbon monoxide indicators are now available on the market which indicate by direct reading of a meter the percentage of carbon monoxide present They are sensitive down to 0 005 per cent and can be estimated to 0 001 per cent (1 part per 100 000)

Treatment.—Emergency treatment requires immediate artificial respiration if breathing has ceased preferably by the prone pressure method It may be employed advantageously for a short while even though the victim is breathing if asphyxia is marked The use when possible of an inhalator for the administration of oxygen or an O_2 CO_2 mixture is most desirable The inhalation of pure oxygen greatly accelerates the release of CO freeing it about four or five times as rapidly as does air A 7 per cent mixture of CO_2 in oxygen is advocated by Drinker and Henderson believes that a 10 per cent mixture is generally not excessive Oxygen alone will however serve admirably With the use of an O_2 CO_2 mixture the blood may be practically freed of CO in approximately half an hour

Patients should not be permitted to make any physical exertion and should be kept warm Seriously poisoned individuals after receiving emergency treatment may well be placed under observation in a hospital Medication and blood transfusions are rarely if ever indicated

W J McConnell

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BENZENE POISONING

Benzene (benzol C_6H_6, to be distinguished from petroleum benzine) is with disturbing frequency, the cause of serious and even fatal poisoning Benzene is obtained by the distillation of coal and the cracking of certain grades of petroleum Prior to the present World War less toxic substances were being substituted in many industrial processes but unfortunately owing to priorities of some of these notably toluol they are being replaced by benzene frequently without warning Benzene is used *widely in the manufacture of rubber goods* and artificial and patent leather, in lacquers paints printing processes as a solvent for fats and greases and motor fuels and for a great variety of other purposes The question *of benzene poisoning has been complicated* by the fact that commercial benzene contains a number of impurities such as thiophene and various homologues of benzene particularly xylene and toluene Extended investigation of the toxicity of such impurities has produced conflicting evidence but the preponderance of opinion favors the belief that they are not responsible for the effects generally attributed to benzene

Etiology—Benzene poisoning is usually caused by inhalation of its vapor though it can be produced by skin absorption Fifteen parts of benzene per 1 000 000 of air may, in some hours produce slight effects and twenty to thirty parts per 1 000 000 may induce coma in susceptible individuals These concentrations are below those frequently encountered in industry but it is now generally held that 100 parts per 1 000 000 should not be exceeded in any working space This latter concentration is accepted by the American Standards Association as the maximum allowable concentration for exposure not exceeding a total of eight hours daily Individual susceptibility to benzene varies greatly for reasons not determined

Morbid Anatomy—Most striking among postmortem findings are multiple hemorrhages throughout the body, uncoagulated blood, abnormalities of the bone marrow spleen and lymph nodes, and evidences of secondary infection

Symptoms—*Acute poisoning* may take place with great rapidity and death ensue in a few minutes Beginning with sudden dizziness the victim may quickly show great muscular weakness and lapse through drowsiness into coma Tremors delirium or convulsions are more infrequent There is often marked dyspnea with possibly, a sense of constriction of the chest, which may proceed to death from respiratory failure The pulse is small and rapid, the skin pallid or cyanotic occasionally showing ecchymoses

Chronic poisoning or subacute poisoning is of much more frequent occurrence manifested usually after days or months of exposure to benzene The early evidences of disease are commonly rather vague such as loss of appetite and weight headache, vertigo and muscular weakness As the condition progresses pallor is marked and is as*sociated with a true anemia* Dyspnea and air hunger may be striking Convulsions and delirium are rare Abdominal pain and gastro intestinal irritation with nausea and vomiting are common Quite typical are hemorrhages from the nose gums bowels kidneys and vagina as well as into the skin and mucous membranes The urine often shows evidences of nephritis with casts albumin, and blood Furunculosis may be encountered and possibly dermatitis related *to skin contact with benzene*

The blood picture may vary considerably from the so called classical changes Leukopenia neutropenia thrombocytopenia hypochromia eosinophilia and anemia may or may not be present Schwarz and Teleky report from their study of recent literature that the tendency now is away from a strict

classification of blood diseases on the basis of the particular blood element involved toward a realization that regenerative activity sets to work in all these cases with greater or less success and the resulting picture depends on the ratio of regenerative activity to the destructive effect of the injurious agent The bone marrow may not be affected or it may be aplastic hyperplastic or leukemic Resistance to infection is lowered

Diagnosis —The use of arbitrary criteria for diagnosis is not advocated The diagnosis cannot be made upon blood findings alone as these may simulate various blood dyscrasias The blood picture of agranulocytosis may be very similar to that produced by benzene and the other well known causes of leukopenia A history of exposure to benzol should be the determining factor in the diagnosis of benzene poisoning Yant and his colleagues report a marked decrease in the percentage of inorganic sulfates of the total sulfates in the urine of workers exposed to benzene They recommend the sulfate test not as a method for diagnosing benzene poisoning but as a reliable indication of benzene exposure

Prognosis —Many seriously poisoned patients have died after several days or weeks others recovering after prolonged illness The mortality among severe cases has in the past been about 50 per cent

Treatment —In acute cases with respiratory failure prompt artificial respiration is indicated The use of oxygen administered with an inhalator is advised Serious blood destruction and hemorrhage are best treated by blood transfusion possibly repeated many times The blood picture should be frequently observed Preparations of liver have been used to advantage Other treatment is symptomatic Because of lowered resistance to infection there may appear complications such as pneumonia bronchitis and cystitis

Prophylaxis involves careful control of industrial processes in which benzene is employed adequate ventilation the selection of healthy individuals as workers with benzene and the periodic examination of persons exposed to the end that those even slightly affected may be removed

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ARSENIC POISONING

Arsenic poisoning is usually the result of exposure to one of the oxides of arsenic such as arsenious acid (As_2O_3) or to arsenical salts such as emerald green (aceto arsenite of copper) or lead arsenate Arseniuretted hydrogen (arsine AsH_3) is highly toxic but produces effects very different from those of arsenic salts Pure metallic arsenic is considered harmless

Incidence —Most industrial arsenic poisoning is seen in workmen engaged in extracting white arsenic (As_2O_3) from cobalt and arsenical pyrites in chemical works glass making cadmium plating in agricultural spraying and dusting in the use of sheep dip or in handling skins treated with arsenic Cases of poisoning have been reported from the use of the organic arsenic compounds from fruit sprayed with arsenic and from certain cosmetics and proprietary remedies

Arseniuretted hydrogen is produced when an acid and a metal either or both containing arsenic are brought into contact with a resulting liberation of nascent hydrogen which combines with arsenic to form the toxic gas Poisoning has occurred in chemical and galvanizing works in submarines

due to arsenic in storage battery plates or acid on ships carrying ferrosilicon which in contact with air and moisture tends to decompose and liberate AsH_3 and in the preparation of hydrogen for balloon inflation

Etiology —Arsenic oxide and the salts are local irritants to the skin and the mucous membranes of the mouth and respiratory passages, inhalation or ingestion of them produces local and systemic changes Acute poisoning is usually due to the use of arsenic with suicidal intent One grain (65 mg) of As_2O_3 has proved fatal Though the normal therapeutic dose of this substance is 2 mg the arsenic eaters of Styria can safely take over 400 mg twice a week

Arseniuretted hydrogen is primarily a hemolytic agent The inhalation of the gas over a period of several hours in a concentration of 30 parts per 1 000 000 will produce poisoning Rambousek claimed that 0 01 mg was highly toxic and the lethal dose as variously stated ranges from 100 mg to over 500 mg There is apparently marked individual susceptibility

Morbid Anatomy —Delepine reported that after poisoning by arsenic trichloride there is found granulo fatty degeneration of the heart liver kidneys pancreas and gastric and duodenal glands After death from poisoning by AsH_3 the liver has been found to be large and edematous with some evidence of fatty degeneration the kidneys large and the renal epithelium degenerated and necrotic Ecker found significant alterations in the nervous system marked by alterations in the ganglion cells and by regions of perivascular necrosis

Symptoms —Arsenic oxides or salts as dusts produce superficially a dermatitis or even ulceration about folds of skin as in the axillae or about the scrotum Increased pigmentation may be noted about the axillae the nipples the eyelids and on the neck Keratosis of the palms and soles may develop after prolonged ingestion of arsenic and skin cancer has been reported to follow the use of the drug The causal relation of arsenic to skin cancer is much disputed Scleroderma was found by Ayres to be associated with exposure to arsenic and to occur in patients who were eliminating arsenic in the urine The septum of the nose in some cases is perforated Legge states that the margins of the cartilage are not involved, and that perforation due to arsenic may thus be differentiated from syphilitic perforation Other symptoms are edema of the lids coryza pharyngitis and laryngitis With more serious poisoning vomiting abdominal pain, and diarrhea may be marked A peripheral neuritis with pronounced paresthesia is moderately common Paralysis similar to that produced by lead may result from the absorption of arsenic, the legs being more notably affected than the arms Tendon reflexes are diminished or lost Diffuse cerebral symptoms such as headache vertigo fatigue drowsiness and impairment of mental activity may result from chronic absorption

Poisoning by arseniuretted hydrogen is manifested usually three to six hours after the gas is inhaled by malaise vertigo weakness headache nausea and vomiting There may be abdominal pain and diarrhea A few hours later hemoglobinuria or hematuria and albuminuria are noted The pulse may become rapid and feeble and the respiration increased The reflexes are exaggerated and there are muscular pains in the extremities Within a day or two jaundice and a coppery cyanosis may be observed The liver and spleen are palpable Oliguria may develop and is of gloomy portent The red blood cells are much reduced possibly to near 1 000 000 the hemoglobin to 20 per cent or less In very severe cases there is a high color index and evidence of extreme blood destruction as well as of regeneration The leukocytes are ordinarily not involved though in some cases there is a slight leukocytosis There develops rarely after several weeks a transitory toxic polyneuritis with pain or anesthesia but no motor involvement

Diagnosis of arsenic poisoning is facilitated by careful inquiry into the nature of the patient s work and by chemical analysis of the urine hair and nails In connection with such analyses it should be noted that normal arsenic frequently has been found in the hair nails and excreta of persons not known to be exposed to arsenic (Schwarz and Deckert) Poisoning by AsH_3 is characterized particularly by the sudden onset, bloody urine and jaundice

Prognosis —Industrial poisoning by ar

senical oxides or salts is rarely fatal Manifestations of the disease may persist for weeks or months Poisoning by AsH_3, if severe is usually fatal within about a week death being due essentially to blood destruction The mortality is approximately 30 per cent Serious damage to the kidneys is almost inevitable and impaired renal function complicates recovery Convalescence is slow

Treatment of chronic arsenic poisoning is largely in the promotion of elimination through the kidneys and bowels In poisoning by AsH_3 oxygen should be promptly administered and the inhalations prolonged Transfusion may be necessary

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MERCURY POISONING

Mercury has long been employed in the arts and in medicine Paracelsus (1493–1541) advocated its use for the treatment of syphilis and Mead (1673–1754) recommended the swallowing of the metal to a pound weight at least in cases of iliac passion in order that by its ponderosity it might restore the natural motion of the intestines

Acute Poisoning —*Etiology*.—Acute poisoning is usually caused by ingestion of bichloride of mercury accidentally or with suicidal intent The absorption of mercury administered therapeutically by mouth injection inunction or in vaginal douches may produce a mild acute or subacute poisoning as does quite rarely, an industrial exposure to massive doses of mercury vapor Ingestion of 0 1 Gm of mercuric chloride may result in acute poisoning although usually 1 Gm or more is required to render the condition serious Mercury is quickly absorbed from the stomach and after brief storage in the liver, is widely distributed

Morbid Anatomy.—In cases dying within twenty four hours of ingestion of mercury there are observed marked gastritis and possibly some nephritis Cases dying within the period from two to seven days after ingestion show a necrotic nephrosis and marked colitis Those dying after one week show a tendency toward healing of the gastric and renal lesions but a severe gangrenous colitis

Symptoms.—The onset is usually rapid within a few minutes after ingestion abdominal pain develops especially in the epigastrium This is fortunately in most cases associated with vomiting and rejection of a portion of the ingested poison There is a metallic taste and often a marked stomatitis and congestion or even ulceration of the pharynx and esophagus The vomitus may early contain blood streaked mucus Stools are loose and bloody There may be prompt collapse and in exceptional cases delirium and convulsions Examination of the blood during the first few days shows blood nitrogen increased the whole blood chlorides reduced and the alkali reserve lowered The urine is strongly acid to methyl red and the renal function is low When the intoxication is not promptly fatal signs of gastro intestinal inflammation and striking evidence of injury to the kidneys usually continue Albumin casts and blood appear in the urine a few hours after ingestion of the poison and gradual suppression of the urine and possibly anuria may be noted The condition may appear very similar to the uremia of chronic nephritis with headache coma and edema

Diagnosis.—It is important to ascertain with certainty that mercury has been ingested In hospital practice many cases treated as mercury poisoning are wholly unproved Some of the newer methods for the determination of mercury are the electrolytic dithizone selenium sulfide spectrographic and photo electric Spectro-analysis

has become a valuable diagnostic aid Small amounts of mercury have been found in the urine and stools of apparently normal healthy individuals

Prognosis —If mercurial salts are vomited within fifteen minutes of ingestion the patient usually recovers The frequent estimation of blood nonprotein nitrogen is of aid in prognosis The majority of deaths occur within the first two or three days The mortality among proved cases may run over 40 per cent though with prompt and thorough treatment in hospital it should be less than 10 per cent If death is not caused by shock or severe gastro enteritis it is usually attributable to kidney damage

Treatment —Emergency treatment may include induced emesis and gastric lavage or treatment of shock The treatment described by Weiss is devised to overcome the effects produced by the poison rather than to provide an antidote to mercury It may be outlined as follows

The stomach is immediately washed with a saturated solution of sodium bicarbonate the operation being continued until the washings are clear At least 2 liters of the solution should be used Before withdrawing the stomach tube 6 ounces of a saturated solution of magnesium sulfate are administered A soapsuds enema is then given As soon as possible thereafter an alkali should be injected intravenously (Fischer's solution crystalline sodium carbonate 10 Gm sodium chloride 15 Gm distilled water 1 liter or a 4 per cent solution of sodium bicarbonate) in quantities as large as 1000 to 1800 cc if there is no disturbing cardiovascular disease Second or third injections should be given on successive days if more than 0 5 Gm (7½ grains) of mercuric chloride was ingested or if there is striking evidence of renal injury

From the onset a beverage made by dissolving 4 Gm (1 teaspoonful) of potassium bitartrate and 2 Gm (½ teaspoonful) of sodium citrate in a glass of water orangeade or lemonade is to be administered six to eight times daily Weiss has seldom used rectal irrigation or hot packs He permits a liberal diet after diarrhea ceases The treatment is controlled by urinalysis and an effort is made to keep the urine alkaline to methyl red

The use of sodium formaldehyde sulfoxalate and of calcium sulfide intravenously has been proposed and there are numerous advocates of sodium thiosulfate Despite the enthusiasm of those who have employed the latter by mouth and intravenously well controlled laboratory studies have failed to demonstrate its utility (Young and Taylor) Berger and his associates believe that except in cases with shock immediate cecostomy with constant lavage is warranted

Subacute poisoning is ordinarily caused by the excessive therapeutic use of mercury The common symptoms—salivation gingivitis and diarrhea—subside upon the withdrawal of the drug

Industrial Poisoning —Industrial mercury poisoning is almost invariably a chronic intoxication resulting from the inhalation of volatilized mercury for a long period One milligram of mercury per 10 cubic meters of air has been proposed as probably the upper limit of safe exposure The most hazardous trades are the production of mercury and its derivatives the manufacture of scientific apparatus (thermometers and barometers), the preparation of hatters fur and felt hat making the extraction of gold and silver by amalgamation, the application of anti fouling plastic paint for the protection of hulls of warships against the growth of aquatic life and the preparation and handling of the fulminate of mercury as a detonator of explosives Since the recent discovery of a substitute for mercury in the treatment of fur certain states by agreement with the manufacturers of felt hats have issued regulations prohibiting the use of mercurial carrot in the preparation of hatters fur or the use of mercurial carroted hatters' fur in the manufacture of hats

Symptoms —Chronic mercurialism has various manifestations far from all of which may be observed in any one case The most typical symptoms are included in the first three of the following groups

1 STOMATITIS SALIVATION a metallic taste reddish brown discoloration of the buccal mucosa gingivitis loosening of the teeth and occasionally a marking of the gums similar to the lead line

2 ERETHISMUS MERCURIALIS a peculiar psychic disturbance characterized by ready excitability and a strange shyness in the presence of strangers a symptom of great interest and importance, insomnia headache vertigo mental depression and dulness and rarely hallucinations

3 TREMORS of the orbit lips tongue fingers and limbs These are usually moderately fine at first but at intervals become a coarse jerking They may become very severe and in rare instances involve contractions of the limbs of such violence as to require restraint The tremor is inten

tional and subsides during rest Under observation it may increase and diminish rhythmically recurring When it is marked the patient may require assistance in eating and in other activities Weakness of both the flexor and extensor muscles of the hand and forearm has been reported but marked paresis is rarely if indeed ever caused by mercury Polyneuritis is said to result occasionally from exposure to mercury There is no ataxia and the reflexes are not notably affected

4 Albuminuria and High Blood Pressure —While the severe nephritis associated with acute mercurial poisoning is not associated with the chronic type these symptoms appear with such frequency as to warrant the belief that the kidneys are usually involved in chronic poisoning

5 Loss of appetite indigestion and diarrhea are occasionally observed There is loss of weight in severe cases The blood is normal except for a moderate secondary anemia

Dermatitis characterized by erythema and desquamation is not uncommonly produced by contact with mercuric chloride or even by ingestion of mercury In susceptible individuals fulminate of mercury produces severe dermatitis Punched-out and penetrating ulcers may develop about the fingernails and knuckles The conjunctivae and the mucous membranes of the mouth nose and larynx are often affected

Prognosis—There is apparently no acquired immunity to mercury The severity of symptoms is usually determined by the length and degree of exposure to the poison While most severe symptoms tend to decrease when the subject is removed from contact with mercury such manifestations as erethism and tremor may persist for a long time Tremor particularly has been observed many years after the last exposure Chronic mercury poisoning is only indirectly a cause of death

Treatment should eliminate the metal through the bowels kidneys and skin The symptoms are relieved by suitable hygiene A diet high in vitamin B complex has been suggested

Mercury dermatitis may be prevented and to some degree relieved by application of a 10 per cent solution of sodium hyposulfite A 2 per cent solution may be used as a wash for conjunctivitis

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CHRONIC BROMIDE POISONING

(*Bromism*)

Bromide therapy first introduced in 1857 has been widely used on account of its sedative action in the treatment of nervous disorders in idiopathic epilepsy and kindred states Self medication with proprietary bromide preparations which are extensively advertised to the public and readily available without prescription is common and it is important therefore that the physician ascertain the extent of previous or simultaneous consumption of these preparations by the patient when prescribing bromides

The bromides are readily absorbed from the stomach when given by mouth and exert a depressing effect on the central nervous system especially on the brain and medulla Their prolonged and indiscriminate use however may cause an intoxication often accompanied with a transitory delirium due to accumulation of bromides in the blood and other body fluids This accumulation is at the expense of the body chlorides which fall in the same proportion and are excreted by the kidney in preference to bromides

Symptoms —The clinical features particularly in the milder forms of bromide intoxi

cation may be somewhat masked by the *underlying disturbance or disease for which* the bromide was administered and the only clue may be an apparent exaggeration of the preexisting illness The patient may complain of headache and dryness of the mouth and show evidence of weakness and in some instances a slight rise in body temperature In the more severe bromide intoxications the symptoms and signs of toxic delirium predominate and are manifested by fear, delusions hallucinations disorientation visual disturbances and disturbances of memory and of equilibrium

Diagnosis —While the symptoms of a toxic delirium may be sufficiently suggestive to permit clinical recognition in a number of cases, a laboratory determination of bromide in the blood should always be made Although a variety of methods for determining bromide concentration has been suggested Wuth s modification of the Walter *Hauptmann method is popularly used* This consists of adding gold chloride to a protein free filtrate of serum and noting a color change in the mixture from yellow to a reddish brown due to the formation of gold bromide For estimation of the amount present the mixture is compared with a standard in a colorimeter or by means of a comparometer

A blood bromine level averaging 200 mg of sodium bromide for each 100 cc of serum is very apt to produce intoxication although susceptible persons may show symptoms with a much lower level and conversely others more resistant may tolerate higher levels with impunity

While admitting the adequacy of the gold chloride method for the initial diagnosis of bromide intoxications Gray and Moore point out certain inaccuracies in the method and suggest that the determination of urine and blood chlorides along with bromides is a far better indication of the progress of treatment or of the validity of a diagnosis

An *acneiform type* of eruption if present is an aid in the diagnosis of bromide intoxication but may be absent in a large proportion of cases

Treatment.—Treatment consists of discontinuing the bromides plus the administration of sodium chloride in doses of 2 to 4 Gm three times daily in addition to that contained in the diet Salt can be pleasantly administered by bouillon cubes, each of which contains 2.5 Gm of sodium chloride Fluids should be moderately forced and the patient should be given a high caloric diet rich in vitamins Bondurant and Campbell have ad*ministered adrenal cortex* extract in combination with sodium chloride to a small group of cases of bromide intoxication and found the combined therapy of value in promoting excretion of bromide and in alleviating bromide effects

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LEAD POISONING

Ever since lead has been used in industry and the arts, lead poisoning has been a well known occupational disease Physicians of the Middle Ages associated colic and *palsy with the poison* but to Tanquerel des Planches (1831) belongs the credit of first correlating all the manifestations of the intoxication It is now known that *the blood* striated and smooth muscle, and the nervous system are most strikingly affected and that the disease is usually associated with inhalation of the dust of lead or of its compounds and with the ingestion of contaminated foods and liquids

Incidence—Although lead poisoning is *still one of the most important* industrial diseases the relative frequency of occurrence is far lower than it was fifteen years ago *Pioneering work of Oliver and Legge* in England and of Alice Hamilton in America

proved that prevention is possible, and as a result of the legislation and factory improvement incited by their investigations the number of cases in industry is rapidly declining About 150 industries involve some exposure to lead The dusty trades are the most hazardous and include the manufacture of white and red lead of storage batteries and of pottery as well as spray painting and fumes from acetylene torch welding

Etiology —Outside of industry lead poisoning is infrequent During prohibition the making of wines and liquors in vessels which contained lead alloys caused some plumbism in the United States Many years ago this was such a common cause of poisoning in the cider district of Devonshire that Devonshire colic became a well known disease In the sixteenth century Colica Pictonum was epidemic in France near Poitiers and later this was found to be caused by the lead added to wine to prevent souring On standing wine thus treated could not turn to vinegar because the lead reacted to form lead acetate

Other less frequent causes of plumbism are the drinking of rather acid water in which lead pipe has been immersed the use of lead salts in hair dyes or cosmetics the chewing of painted surfaces by children and the ingestion of lead salts with suicidal intent or to cause abortion The amount of lead which enters the organism need not be large to produce severe symptoms as is shown in a case of poisoning reported after the ingestion of 1.33 Gm of lead acetate (less than 750 mg of metallic lead)

It is now known that lead may be absorbed from the gastro intestinal tract from the respiratory tract and even from the mucous membranes of the nose and mouth The respiratory tract is the more dangerous path of entry because inhaled lead dusts may enter rapidly into the circulation and so become widely distributed while most of the lead absorbed from the gastro intestinal tract is caught by the liver and excreted back into the duodenum Subcutaneous or intramuscular deposits of lead enter the blood stream so very slowly that intoxication from bullets if it occurs at all is very rare Absorption of inorganic lead salts from the skin is probably negligible though there is a source of danger from some organic compounds, such as lead tetra ethyl which are soluble in lipoids

Lead is a cumulative poison because it is stored in relatively large amounts in the solid portion of the bones Until it is liberated from the skeleton this deposit does no harm During absorption the blood stream carries lead to all the organs, especially to the bones liver kidneys and intestines After active absorption has ceased, almost all the lead in the body (more than 95 per cent) is to be found in the bones from which it is excreted extremely slowly Symptoms of lead poisoning may appear when lead is circulating in sufficient concentration throughout the organism as a result either of absorption from outside sources or of liberation from the deposit in the bones

Lead is excreted through the gastro intestinal tract and the kidneys The larger part of lead eliminated is in the feces but the fact must be kept in mind that during active absorption of lead the feces also contain some which has been ingested but has never been absorbed The amounts of lead excreted in urine are usually very small

Morbid Anatomy —Some claim that an abnormally high incidence of arteriosclerosis chronic interstitial nephritis gastric ulcer and cirrhosis of the liver are found in lead workers None of these is established except nephritis which is rare and a late manifestation In permanent palsy many of the anterior horn cells in the cord disappear The affected muscles are atrophic and fatty and the muscle tissue itself is gradually replaced by fibrous material There are no other definite pathologic changes except after lead encephalopathy in children when cerebral atrophy may result

Symptoms —*Acute Poisoning* —True acute poisoning is to be seen only after the sudden ingestion of large doses of lead and is very rare The symptoms are vomiting and collapse and there may be a peripheral destruction of large quantities of red blood cells accompanied by acute anemia and sometimes by hemoglobinuria The marked general weakness loss of appetite diarrhea dehydration and epileptiform convulsions may result in death or in a more chronic type of poisoning This should not be called acute lead poisoning because the symptoms are those of the more chronic type

Intoxication —In chronic plumbism the patient usually suffers from weakness lassitude obstinate constipation and often from intense colic A peculiar pale pasty appearance of the skin is quite characteristic of the condition The several features peculiar to lead intoxication will here be considered individually

(*a*) CHANGES IN THE BLOOD —One of the earliest evidences of lead poisoning is a change in the nature and number of red cells in the circulating blood A marked destruction of erythrocytes in the peripheral circulation is accompanied by increased production of red cells The counterbalancing of



Fig 47—Palsy of the Aran Duchenne type due to lead poisoning

the loss of red cells by stimulation of bone marrow activity maintains the cell count above 3 500 000 or 4 000 000 cells per cubic millimeter so that anemia is usually not so severe as the pallor of the patient would suggest Recent investigations of the mechanism of destruction of blood have shown that lead reacts with inorganic phosphate to form insoluble lead phosphate and acid on the surface of the cells This renders the cells inelastic and brittle so that they are broken more easily than normal cells by the traumata suffered in circulation

The most characteristic change in the blood is the appearance of "stippling" a *punctate basophilic* granulation in the cells which is best demonstrated by dilute Unna's alkaline methylene blue stain This may continue for some months after absorption of lead has ceased Stippled cells are probably degenerating young reticulated cells Their presence in the blood is not absolutely pathognomonic of lead poisoning as a few may be found in cases of pernicious anemia leukemia severe infections, particularly in children, and in normal blood, but there are *more than 1000 stippled cells* per million *red cells* in the chronic type of lead and radium intoxication An increasing stippled count usually precedes the onset of a toxic episode as it indicates a damage to body cells Stippling is therefore one of the reliable criteria for establishing the diagnosis of lead intoxication

(*b*) THE LEAD LINE —The "lead line" on the gums is a second important sign of plumbism and is very valuable in making a diagnosis It is due to a deposit of lead sulfide about the blood vessels in the tips of the papillae and therefore appears most plainly about pyorrheic gums When examined with a lens it has a punctate appearance A piece of paper inserted between the gum and tooth distinguishes stippling from staining of the tooth root The peculiar localization differentiates this from the other pigmentations of the mouth which are more diffuse The lead line is practically pathognomonic of lead absorption but not of poisoning It may persist for many months after exposure to lead has ceased It must be distinguished only from the similar line produced by bismuth

(*c*) COLIC —Abdominal colic is the usual manifestation of lead intoxication It is usually preceded by constipation and indefinite abdominal pain While the character of this colic in individual cases varies greatly it is usually very intense and prolonged The pain which is generally felt below the umbilicus is often relieved by pressure During attacks the abdomen is scaphoid in shape not tender to pressure and while resistant shows no evidences of true abdominal muscle spasm Paroxysms of pain occur when peristaltic waves approach areas of marked tonic spasm in the intestines This lead colic is often very difficult to differentiate from an acute abdominal inflammation but diagnosis

is aided usually by *other signs of lead poisoning* It should be remembered that in lead poisoning the white count is only slightly increased if at all that there is a relative lymphocytosis and no fever While intestinal colic is the usual manifestation similar attacks have been described in any viscus composed of smooth muscle

(*d*) Palsy —Palsy has been recognized as one of the symptoms of lead poisoning for many years Although in 1834 Tanquerel des Planches reported that it occurred in 10 per cent of the 1200 cases he had examined it is now relatively rare because of improvements in industrial management A general weakness and tremor of fatigued *muscles usually precede the actual onset of* paralysis These may well be demonstrated by extending and actively spreading the fingers They have been shown by Steiman to be associated with difficulty in resynthesizing creatine triphosphate The paralysis which may follow if lead exposure continues is similar to peripheral neuritis and is usually rapid in onset and painless One of its very striking characteristics is its marked localization in the most used and fatigued muscles the extensors of the wrists and fingers of the dominant hand are first attacked in a startlingly specific manner producing the characteristic finger and wristdrop and leaving flexor and pronator muscles uninvolved Paralysis may also appear in the peroneal muscles of the legs and produce a steppage gait Optic neuritis has also been described After absorption of lead stops muscle weakness requires weeks but true palsy requires months for a return of function If exposure to the poison continues paralysis may be permanent and progressive

(*e*) Psychosis —In many cases of lead poisoning there is mild mental depression while occasionally transient delirium and convulsions occur Rare cases show severe cerebral involvement characterized by marked delusions *and mania leading to convulsions* and death This psychosis may closely simulate general paresis in its clinical manifestations although the Wassermann *reaction* is not positive The spinal fluid shows only an elevated pressure

Lead poisoning is usually made manifest in children by epileptiform convulsions This is particularly serious as it may result in *death or in subsequent mental retardation* with cerebral atrophy

(*f*) Gout —In England gout is frequently reported in chronic cases It is certainly extremely rare in America

(*g*) Degenerative Changes —That the late manifestations of lead poisoning are largely degenerative and are caused by the continued action of the lead stream is said to be shown by the occasional appearance of arteriosclerosis contracted kidneys and a resulting high blood pressure and hypertrophy of the heart All of these manifestations however seem no more common in lead workers than in the average individual

Diagnosis —The diagnosis of lead poisoning *is often difficult because evidence of ab*sorption without signs of actual intoxication may frequently be observed Usually unless at least two symptoms characteristic of the poisoning appear a definite diagnosis of plumbism should not be made The best evidence of intoxication is marked stippling of the red cells but lead line colic constipation anemia muscle weakness and wrist drop are also important In children the epiphyseal ends of the bones disclose a dense line by x ray After union of the bone epiphyses no lead line in bone can be found by x ray The excretion of lead in the urine and feces is also significant though it is found in the urine in many individuals not known to be exposed to lead The greater part of the lead excreted is to be found in the feces but its presence is of little diagnostic value unless all possibility of swallowing lead has been removed Lead in the urine however gives an index of the amount of exposure to lead Up to 0 08 mg per liter is considered a normal amount This level rises higher as lead exposure increases and symptoms are apt to appear when urinary lead is above 0 2 mg per liter This proves that lead has been absorbed by the organism but is not in itself a proof of intoxica*tion*

Final diagnosis depends upon all of these considerations but usually requires at least two of the described features In some cases both the lead line and slight stippling appear in workers without other evidences of poisoning but marked anemia colic or nervous lesions are usually deciding factors in diagnosis

Lead poisoning often appears after prolonged exposure but occasionally even after exposure has ceased This tardy development of symptoms is probably caused by liberation of the lead deposit in the bones which occurs during severe illness or alcoholic debauches It has also been once reported after taking potassium iodide Thus if lead is held harmlessly within the body some change in the general metabolism may precipitate an attack of poisoning The disease should always be thought of in acute abdominal crises as it not infrequently is the cause of unnecessary surgery

Prognosis —The prognosis depends upon the type of symptoms Colic usually disappears within a few days with suitable treatment while anemia constipation and general debility remain for weeks Palsy disappears very slowly and in some cases is permanent Severe psychoses are often fatal but those patients who survive rarely show chronic psychoses usually these disappear promptly and completely The mild depression which is so common a symptom is lost as other acute symptoms subside The encephalopathies of children may lead to mental deterioration

Prophylaxis —Dust and fumes are the most common sources of poisoning at the present time If proper precautions are taken by workmen and employers to avoid all dust hazards by suitable ventilation aided by the use of respirators intoxication may be very largely prevented The incidence of poisoning among painters may be greatly reduced by the use of sandpaper which can be moistened Clean hands and clean places to eat must be insisted upon The toxicity of lead varies so much with individuals that no definite prediction may be made as to the amount which will cause symptoms of poisoning to appear although Legge states that a continued absorption of more than 2 mg per day may produce intoxication

Treatment —Relief of the severe colic of lead poisoning often demands much medical ingenuity Intravenous calcium gluconate or calcium chloride usually gives prompt relief for several hours Atropine in large doses or nitroglycerin may also be tried A hot water bottle may be comforting If diagnosis is certain a saline *cathartic* or an *enema* is also desirable *Morphine* is rarely necessary to relieve the pain

After the subsidence of acute symptoms the purpose of the treatment is to gradually eliminate lead from the body Since it was first recommended by Melsens in 1840 *potassium iodide* has been employed to increase the excretion of lead The initial doses should not exceed 1 Gm per day, and the amount should then gradually be increased

A more effective *method of treatment* has been developed which is dependent upon the parallel metabolism of lead and calcium (Aub and Minot) Thus it is probable that storage of lead may be reduced by keeping the bones filled with calcium by means of an adequate intake of milk When patients are suffering from lead colic a prompt relief may be obtained by the slow intravenous injection of 10 cc of a 20 per cent sterile solution of calcium gluconate After the pain has been relieved by this method a strenuous cathartic is given In acute cases a diet containing much calcium should be given This consists of 1 to 2 quarts of milk and 6 to 8 Gm of calcium lactate daily it tends to reduce the circulating lead After disappearance of acute symptoms such a diet should be replaced by one containing as little calcium as possible (No milk eggs nor green vegetables) With this large doses of ammonium chloride should be given to accentuate the negative calcium balance and thus tend to liberate lead from the bones This should be continued for four to six weeks Recent therapeutic suggestions have included the use of vitamin C and also the use of citrate to lower ionization and to maintain solubility of lead in the blood stream

Saline cathartics have long been recommended to relieve constipation They probably do not increase the excretion of lead Treatment for the *anemia* of lead poisoning should be like that for any secondary anemia *Palsy* best responds to galvanic current and massage and should be treated like a peripheral neuritis Disappearance of the acute symptoms of plumbism does not signify that the disease is cured Treatment to stimulate elimination of lead and to regulate the bowels should be continued for some weeks after the more distressing symptoms have been alleviated

It is always desirable for a patient suffering from any of the symptoms of lead poisoning to avoid further exposure to lead

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RADIUM POISONING

Definition —The term radium poisoning should be restricted to the harmful effects caused by the swallowing inhalation or injection of radium mesothorium or other long lived radioactive substances Radium poisoning is similar to lead poisoning in that in both conditions there are actual deposits of the heavy metals (radium or lead) in the body tissues

There are also deleterious effects produced by radium (and x rays) which do not constitute radium poisoning but because such injuries may produce leukopenia anemia and even death they are closely allied to radium poisoning These conditions result from undue exposure to external penetrating noncumulative radiation given off by these physical agents and include the occasional harmful effects of radium or x rays applied externally in the treatment of cancer or other conditions and from the industrial use of both radium and x rays in the examination of castings and steel armor

History.—Radium poisoning was unknown until 1925 when Martland and his coworkers reported deaths among dial painters formerly employed in a New Jersey plant. These workers while painting luminous watch dials pointed their brushes in their mouths and swallowed small amounts of radium paint The symptoms diagnosis during life and after death autopsy findings microscopic pathology toxicology and treatment were described for the first time and the existence of radium poisoning definitely established

Etiology —The *ingestion of radioactive luminous compounds* by workers painting luminous dials on watches and clocks has been the main source of radium poisoning This danger practically ceased in 1925 when workers stopped licking their brushes and there was a lessened demand for watches with luminous dials The great increase in aviation however during the past few years and the requirements of the Second World War have created an enormous demand for luminous dials especially for navigation purposes For example a large bomber may have 100 dials in the cockpit with the equivalent of more than 400 micrograms of radium Thus the dial painting industry again employs hundreds of new operators Furthermore no satisfactory mechanical method of applying the radium paint has been found Nor is the elimination of radium paint feasible since the glare of an artificial source of light would make accommodation difficult for night flying and furthermore this might be shot away

Dial painting has therefore again become an important hazard and every protective device must be used to prevent radium poisoning In spite of all precautions recent examinations of a large number of dial painters most of whom have worked at this occupation for less than two years revealed that more than 7 per cent of the girls have already accumulated dangerous deposits of radium in their bodies

Other occupational exposures to radioactive substances occasionally occur In the *mining of radium* there is less risk than in the *refining* of the product The chief dangers are the *inhalation of radon* and radioactive dust from the ores and early products of extraction

Chemists physicists laboratory hospital and other workers exposed to radioactive substances may also develop radium poisoning, through inhalation or ingestion of emanation or dust However, the main hazards are refining of radium and mesothorium, the tubing of partly aged radium material the preparation of luminous paint needles plaques and containers, the explosion of bombs or radium apparatus containing highly concentrated emanation, the dusting of dishes etc The possibility of direct bomb hits on large emanation plants during air raids must be considered but most of these dangers can be avoided by proper protective measures

Drinking of *artificial waters containing radioactive salts* (radium waters) has caused a number of deaths The use of such waters is extremely dangerous and must be prohibited

Drinking of *artificial waters containing only the gas emanation* (radon waters) is thought to be harmless since most of the gas escapes quickly At least there is no proof that they have produced radium poisoning This group includes waters charged by various crocks emanators and activators

Further drinking of *natural spring waters which contain only emanation* is not considered dangerous Beneficial results of treatment at radioactive spas are due largely to the psychic effect and the regular hygienic habits of the patients There is no scientific basis for the therapeutic use of any of these waters or baths because of their radioactive properties

Patients may be poisoned by radium and radioactive substances unwisely employed for therapeutic and diagnostic purposes Intravenous injections of the soluble bromides and chlorides of radium have been used for almost every ailment especially gout rheumatism senility cancer and leukemia As there is a lack of direct evidence of their curative value in any medical condition the therapeutic injection of radium or radioactive salts is unwarranted and is distinctly dangerous because of the cumulative effects

The diagnostic use of *thorium dioxide solution by intravenous injection* for roentgen visualization of the liver spleen and arteries and its injection into the brain or various sinuses have all been described despite repeated warnings of its radioactivity and toxicity Observation of patients for one or two years is insufficient since harmful effects may occur after a much longer period Animal experimentation has shown that thorium dioxide causes hepatic necrosis and cirrhosis and sarcomas have been produced in mice and rats by subcutaneous and intraperitoneal injections

Recent advances in physics especially with the development of the cyclotron have led to the induction of radioactivity in nearly all the elements Such radioactive elements when injected behave as tagged atoms but chemically resemble their inactive relatives Acting as tracers these may furnish important data in cell metabolism Their selective deposition in the tissues (phosphorus in bone iodine in the thyroid) introduces a new method of selective irradiation which may prove useful in the treatment of cancer leukemia and allied conditions The injection and use of such *artificial radioactive substances* would theoretically at least be harmless since most of the radiation from these substances is *short lived* (minutes hours or a few days)

Toxicology—When radioactive substances are ingested over a long period very small amounts enter the circulation That portion not excreted is constantly subjected to phagocytosis by the cells of the reticulo endothelial system in the liver spleen and bones

In time the liver and spleen rid themselves of these deposits and eventually over 98 per cent of the radium not eliminated is stored in the bones as carbonates, phosphates and even sulfates

The toxic effect of radium when deposited in the bone is due entirely to its radiations consisting in large part *(92 per cent)* of alpha rays the effect of the small amount of beta and gamma radiation is practically negligible This incessant alpha bombardment irritates the bone marrow and its blood forming centers

A similar storage eventually occurs after *the inhalation or intravenous injection* of radioactive substances with the exception that when the respiratory tract is the portal of entry the lungs may show considerable radioactivity

Morbid Anatomy —The tremendously disruptive effect of the alpha particle causes atomic and molecular disintegration within the tissues In time irritative stimulation sets up a hyperplastic red marrow characterized by a packing of the spaces with primitive stem cells Megaloblastic erythropoiesis is a prominent feature and the peripheral blood often resembles addisonian anemia With the exception of eosinophilic myelocytes which are numerous granulopoiesis is greatly impaired Hence leukopenia with an agranulocytic syndrome is seen in some cases This hyperplastic irritative embryonal marrow is the *first stage of radiation osteitis*

After a period of months or years the process subsides in patchy areas over the skeleton and an intensely inflammatory and very cellular replacement fibrosis develops This is the *second stage of radiation osteitis* Many of the fibroblasts show mitotic figures and hyperchromatism and these areas can be distinguished from sarcoma only with great difficulty *It is in these areas that sarcoma undoubtedly arises*

In radium poisoning the radioactive deposits act as *carcinogenic agents* and must be added to that rapidly growing list of agents now known to produce cancer All such agents induce cancer only after a lapse of time which occupies a *considerable fraction of the normal span of life* of the individual or experimental animal In human beings suffering from radium poisoning it usually takes ten or more years for bone sarcomas to develop and in experimental rats more than one year is required

The *bone tumor* characteristic of radium poisoning is an *osteogenic sarcoma* of the medullary and periosteal variety although periosteal fibro arcomas have been observed Because of their anaplastic qualities and rapid growth however many are predominantly osteolytic and in these bone formation may often be scant

Most of the bone sarcomas have occurred in dial painters who swallowed radium paint They have also been caused by the drinking of radium water containing salts in solution and after intravenous injections

If however the portal of entry has been the respiratory tract such as occurs from undue inhalation of emanation and radioactive dust *primary carcinomas of the bronchi* may develop Examples of these are seen in the miners of Joachim tal and Schneeberg and in physicists who have died from lung cancer Bone tumors in these cases have not been observed since the chief deposits have been in the lungs

The *third* or *final stage of radiation osteitis* is one of healing with almost entire subsidence of all inflammatory reactions The marrow is entirely replaced by an old noncellular fibroblastic tissue The bones become soft partially decalcified and crippling bone lesions occur

Symptoms —Radium poisoning is a slow insidious chronic disea e and after exposure the patient may remain in good health for many years before clinical symptoms occur

In rare instances massive doses of radioactive substances especially thorium X have been followed by *acute radium poisoning* and severe fatal anemia

Patients having relatively large amounts of radioactive substances deposited in their bodies (the equivalent of 20 to 180 micrograms of radium) usually develop extensive radiation osteitis throughout most of their bones within one to five years A superadded bacterial infection from the teeth often leads to extensive necrosis of the mandible and maxilla Anemias of the regenerative pseudo aplastic or pernicious type may develop The usual type of anemia is clinically difficult to differentiate from the refractory anemias of the aplastic type (the marrow however is hyperplastic) Hemorrhages from the mucous membranes and intestinal tract are unusual Most of these cases die as the result of extensive jaw necroses the severe anemias and from terminal sepsis

Patients having smaller amounts of radioactive substances in their bodies (the equivalent of 2 to 20 micrograms of radium) usually escape the extensive jaw necroses and anemia but develop crippling bone lesions usually within eight years Coxa vara deformities of the spine moth eaten lesions of the flat bones of the skull and spontaneous fractures are most frequently encountered

Some old cases lose most of their radioactivity but still suffer from crippling lesions due to extensive decalcification However definite bone destruction and bone sarcoma

have been noted with as little as 0.5 of a microgram of radium in the entire body

The symptoms directly attributable to the sarcomas are identical with those produced by ordinary sarcoma of the bones Diagnosis depends upon the presence of a bone tumor as shown by x rays and proof that the victim is radioactive The prognosis and treatment are the same as those of any malignant bone tumor Since many radium sarcomas remain localized for a long time amputation should be seriously considered

Diagnosis —Whenever there is a history of industrial or occupational exposure to radium or other radioactive substances or of their therapeutic use or their injection for diagnostic radiographic purposes the possibility of radium poisoning exists

Radium poisoning can only be *proved* by the demonstration of radioactive deposits in the body in amounts greater than what is now considered the *tolerance dose* (the equivalent of 0 1 microgram of radium in the entire body)

In order to recognize radium poisoning in its inception long before clinical symptoms appear and at a time when further exposure may be stopped and elimination therapy used to best advantage very sensitive methods of testing are required since amounts far below the tolerance dose of 0 1 of a microgram must be detected

The original electroscopic methods were seldom able to detect with any degree of accuracy deposits of radium less than 5 micrograms Such methods are now obsolete

Gamma ray detectors employing highly improved Geiger Mueller tubes are much more sensitive but body deposits below 0.5 of a microgram are difficult to record and surface contamination of the body cannot always be eliminated as a source of radioactivity

At the present time the only method that will meet the requirements is the *Expiratory Breath Analysis of Evans* This method requires specially constructed nonportable apparatus and can only be performed by competent physicists trained in modern methods of radon and thoron analyses The expiratory air may be collected in special containers and shipped to the laboratory

Radium poisoning cannot be diagnosed from an examination of the blood Most of the profound anemias develop only in the terminal stages of the disease in individuals who have comparatively large radioactive deposits in their bodies Periodic blood examinations are of little value since small deposits may stimulate blood formation and blood counts of radioactive individuals be higher than those of the average industrial worker

The roentgenographic study of dental films for jaw necroses and the skeleton for evidence of radiation osteitis and malignancy is of great diagnostic importance in well advanced cases of radium poisoning

Treatment —No specific treatment so far advanced is of aid in long standing cases of radium poisoning especially those patients who show appreciable amounts of radioactivity and suffer from destructive bone lesions

In such cases extensive dental operations are contraindicated for they may result in intractable jaw necrosis When anemia develops therapeutic measures are of little value

In early cases long before clinical symptoms appear *decalcification therapy* consisting of a low calcium diet along with periodic administration of ammonium chloride parathyroid extracts and magnesium gluconate may be of some value for at this time the trabeculae of the bone contain some eleven times as much radium as the cortex and the radioactive substances are more accessible for mobilization and elimination

In older cases decalcification methods are of little value for the deposits are fixed in the cortex of the bone and the amount of radium excreted under this form of treatment is a very small fraction of the total stored radium

Prevention —No long lived radioactive substances in any form should ever be introduced in the human body because of the danger of radium poisoning

In industry all measures should be taken to eliminate or reduce to a minimum the swallowing of radioactive substances the inhalation of radon thoron or radioactive dust and external exposure to gamma radiation coming from large amounts of radium or from x rays

Such procedures should include the proper selection instruction and supervision

of personnel including cleanliness in the worker and work rooms forced ventilation of hoods and work rooms and other pre cautions

In addition, periodic medical and dental examinations including periodic radon or thoron analyses of the expired air and blood examinations for the detection of leuko penias anemias or any other abnormalities must be enforced

To protect the worker exposed to radium or other radioactive substances against radium poisoning and also any harmful ef fects from external noncumulative expo-sures to radium three important technical procedures should be carried out

1 To detect early minute radioactive deposits in the worker s body and to pre-vent further accumulations the *expired air* should be tested once a year or more often if necessary

When the radon analysis of the expired breath of any worker indicates the equiva lent of more than *0 1 of a microgram* of radium in his body (1 micro microcurie per liter of expired air) he should be removed from further exposure and treated by de calcification therapy or any other modality which may have been developed for this purpose

2 To avoid inhalation of dangerous amounts of emanation general forced ven tilation should be provided for all work rooms so that the radon concentration of the air does not exceed *10^{-11} curie per liter* at any place at any time Experience has shown that this is easily obtained in mod ern plants

3 To avoid undue exposure to gamma radiations coming from large amounts of radium in near vicinity of the worker it is important that the whole body exposure shall not exceed 0 1 roentgen per working day

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THE INTOXICATIONS

ALCOHOLISM

Definition—Alcoholism denotes the state of the body following the ingestion of relatively large amounts of ethyl alcohol The sequelae of alcoholism depend on whether it is acute or chronic

Acute Alcoholism —*Definition* — The acute effects of alcohol depend primarily on its action on the central nervous system The definition of the state of drunkenness is difficult According to Purves Stewart a drunken person is one who has taken alcohol in sufficient quantity to poison the central nervous system producing a temporary disorder of the faculties so as to render him unable to execute the occupation in which he was engaged at the time thereby causing danger to himself or to others

Physiology—Alcohol is freely absorbed not only through the gastro intestinal canal but also through the lungs following inhalation It is quickly taken up after subcutaneous and intramuscular injection Alcohol is also freely absorbed from the rectum and the colon Thus severe intoxication may develop through accidental use of alcoholic solutions as in enemas Through the skin the absorption is slight unless there is inflammation or abrasion In the gastro intestinal tract slight absorption may occur even through the mucous membranes of the mouth A considerable degree of absorption takes place in the stomach and in the small intestines which readily absorb any alcohol that reaches them

The rate of intestinal absorption depends on the concentration of the ingested solution as well as on the intestinal contents The presence of food material particularly fatty substances delays absorption Habituation is apparently also a factor as it has been shown that absorption is more rapid in persons unaccustomed to drinking than in habitues

The distribution of alcohol in the tissues depends on the time interval between ingestion and analysis Following complete absorption distribution is fairly even in the tissues Concentration is high in the brain and low in the bones Alcohol has a caloric value of 7 calories per gram It is rapidly oxidized to carbon dioxide and water and it is estimated that in man between 5 and 10 Gm of alcohol are oxidized per hour At times some intermediary metabolite may appear in the blood The amount of excretion of alcohol depends on the intake but as high as 10 per cent may be eliminated in the urine sweat and other secretions Whether true tolerance occurs either in the form of increase in the oxidative capacity of the tissues or in the form of increased resistance of organs to the same amounts of alcohol is not definitely established

Following a single ingestion of alcohol the maximal level in the blood is fairly evenly maintained for about five hours The concentration of alcohol in the urine closely parallels that in the blood unless there is great delay between urine formation and emptying the bladder There is a rough correlation between the concentration in the blood and urine on the one hand and the clinical behavior on the other A concentration under 100 mg per 100 cc is generally not accompanied by symptoms Manifestations of exhilaration are usually associated with a concentration of from 100 to 300 mg and depression and severe ataxia with a level of 400 to 500 mg Above this level coma is frequently present A concentration of from 700 to 1000 mg usually causes death

Morbid Anatomy—When death is directly due to ethyl alcohol no specific gross or microscopic lesions are detectable Hence the cause of death cannot be determined from the morphologic findings Positive evidence can be established only through chemical analysis of the brain and other tissues The clinical history and postmortem findings nevertheless provide weighty indirect evidence There is usually an intense degree of postmortem lividity over the dependent portions of the body The mucous membrane of the stomach is frequently but not invariably congested or hyperemic and

punctiform hemorrhages or superficial erosions may be present The brain immediately after opening of the skull usually has a slightly aromatic odor Frequently there is some degree of edema of the pia arachnoid and of the parenchyma itself At present however no characteristic changes in the brain are known to exist Edema of the lungs occurs in many instances The right chambers of the heart may be distended The spleen liver and kidneys except for some congestion show no striking changes If cirrhosis of the liver is present this cannot be related to the acute use of alcohol

Symptoms—A small or a moderate amount of alcohol taken in the form of a beverage produces a general sensation of well being exhilaration and boosting of the ego This first stage of excitation depends primarily on removal of the inhibition of the higher centers After ingestion of larger amounts the functions of the higher centers become further disturbed and manifestations of depression of the central nervous system appear Judgment and capacity for observation become impaired and an increasing degree of euphoria develops Gradually reflex irritability is decreased and muscular incoordination develops If the consumption of alcohol continues sensory disturbances such as diplopia tinnitus aurium and numbness gradually appear The pupils often become dilated or in rare instances constricted and they may become unequal The face is generally flushed Frequently there is nausea and vomiting The pulse is full and the heart rate rapid The arterial pressure is somewhat lowered At this stage a marked degree of ataxia is usually present The subject may be unable to stand or even to sit up Gradual impairment of consciousness occurs often accompanied by incoherent muttering At times coma appears with unexpected rapidity The respiration is slow and stertorous and the breath smells strongly of alcohol or of the beverage consumed Circulatory collapse disturbance of heat regulation with lowered temperature acute urinary retention or incontinence of urine and feces may develop Such a degree of intoxication is dangerous and death may occur either with unexpected rapidity or following many hours of deep coma Severe reactions are enhanced by exposure to cold weather

In rare instances individuals who have taken moderate amounts of alcohol do not appear drunk but exhibit a type of automatism They may go about their daily work in an automatic fashion or they may wander away Frequently such individuals subsequently exhibit amnesia Their condition is called *alcoholic trance* or *alcoholic automatism* It depends primarily on psychic aberration of the patient and alcohol is merely a precipitating factor

Dipsomania is a special form of periodic acute alcoholism associated with emotional difficulties and maladjustment At times this tendency is inherited With an uncontrollable urge the subject goes on a spree Between attacks he is rather quiet and often subdued and exhibits no craving for alcohol Following the spree patients often experience intense remorse and depression They may attempt suicide Dipsomania is primarily a psychologic and social problem

Complications—Among the immediate complications of acute alcoholism are severe postalcoholic headache lassitude and dehydration Patients in alcoholic coma may subsequently develop lobar or bronchopneumonia from aspiration of food material or as a result of exposure If the coma is of long duration collapse and shock may supervene Following recovery some patients develop persistent vomiting which results in dehydration and circulatory collapse At times during forceful retching longitudinal lacerations at the junction of the esophagus and the cardia develop leading to severe and even fatal hemorrhage Jaundice caused by acute changes in the parenchyma of the liver at times follows alcoholic debauches Acute pancreatitis may develop secondarily and probably is related to vomiting and to regurgitation of intestinal contents in the pancreatic duct Nephritis may result from certain types of contaminations in the liquors Acute generalized distention of the abdomen imitating peritonitis or intestinal perforation and at times acute mania or convulsions can complicate the picture of intoxication Alcoholic intoxication is apt to bring to the surface underlying psychic abnormalities and conflicts If acute appendicitis or intestinal perforation occurs dur

ing alcoholic intoxication, it may give symptoms only when the patient has recovered from the alcoholic debauch

Among the complications of acute alcoholic intoxication mention should be made of its relation to exposure to venereal disease Finally acute alcoholism has an important bearing on the commitment of misdemeanor and crime Meyer states that in Massachusetts arrests for alcoholic intoxication in 1923 constituted 47 per cent of all arrests and in 1930 33 per cent

Diagnosis—This is usually not difficult if a history is available Nevertheless mistakes are not uncommon particularly with patients who are in coma The usual diagnostic errors involve fractured skull subdural or subarachnoid hemorrhage cerebrovascular accident uremia and diabetic coma Special caution should be exercised in diagnosing the condition of unknown patients brought to the hospital by the police In difficult cases, correct diagnosis will depend on the successful search for a history on a knowledge of the differential characteristics of coma of various etiology and on the laboratory findings

Prognosis—This depends on the amount of alcohol consumed and on the types of complications Acute alcoholic intoxication without coma usually disappears spontaneously The presence of coma however, offers a more serious prognosis Certain complications may seriously interfere with the recovery of the patient

Treatment—Usually no special treatment is required, as the subject sleeps off the intoxication Patients in alcoholic coma however require careful nursing supervision Gastric lavage should be performed promptly If the body temperature is subnormal and there are indications of collapse heat can be supplied effectively by irrigation of the stomach with warm saline solution The head should be lowered to prevent the aspiration of gastric contents Inhalation of a mixture of 5 or 10 per cent carbon dioxide and 95 or 90 per cent oxygen is effective in stimulating the respiration and hastens awakening Intramuscular administration of from 10 to 15 grains (0 75–1 Gm) of caffeine sodium benzoate or of a coffee enema will serve the same purpose Ephedrine sulfate administered intramuscularly in doses of ½ grain (30 mg) every two hours may be effective in awakening the patient The position of the body should be changed frequently in order to prevent hypostatic pneumonia In acute mania subcutaneous injections of apomorphine in doses of $\frac{1}{10}$ to ⅙ grain (6–10 mg) have been used effectively Apomorphine however can cause acute depression of certain vegetative nervous centers In the treatment of postalcoholic headache and dehydration fluids containing sodium chloride or mineral salt mixtures are useful

Chronic Alcoholism—*Definition*—A large number of persons who indulge in the chronic use of alcoholic beverages suffer from psychic and bodily consequences Persons given to this habit are nervously unstable and feel an irresistible urge to drink Since such an urge may arise entirely from disturbance of the psyche the medical problem of chronic alcoholism is primarily of psychiatric nature In spite of the fact however that the cause of chronic alcoholism is often psychogenic its consequences can be manifested in disturbances of numerous functions of the body Chronic alcoholism has also an important bearing on the clinical course of a number of diseases The various bodily effects produced by the frequent ingestion of moderate amounts of alcohol or by irregular bouts of drunkenness are collectively called "chronic alcoholism

Etiology—The immediate cause of chronic alcoholism is previous experience with acute intoxication Whereas some individuals go through such an experience without developing a special urge to repeat it others develop an addiction Many individuals suffering from chronic alcoholism exhibit unstable nervous systems and they are from a psychological point of view, inferior personalities Frequently the personality of the addict plays a more important role than the alcohol itself Chronic alcoholism is primarily a problem of psychiatry

Physiology—The immediate effects of the chronic ingestion of alcohol in the habitue are fundamentally the same as those produced by acute ingestion of nonhabituates There is some evidence indicating that the oxidation of alcohol may be more rapid in the chronic alcoholic Constant repetition of the same stimulus or insult may however

produce effects of far reaching consequences The chronic local effects of alcohol on the mucosa can lead to an inflammatory process (chronic gastritis) and this in turn may affect a number of digestive processes In view of the fact that alcoholic beverages are rich in calories but poor in vitamins and other essential food substances certain nutritional deficiencies are particularly apt to develop This tendency is further accentuated by the anorexia and gastric distress common in chronic alcoholics The demoralizing effect of constant conflict with society at large is also a factor that bears on the change in the nervous functions

Some of the manifestations attributed to chronic alcoholism are not due to ethyl alcohol but to admixture of substances such as ether acetaldehyde essential oils and lupulin of the hop The *convulsive seizure* observed following the chronic use of absinthe or vermouth probably depends on the action of oil of wormwood The adulteration of whisky with *triorthocresol phosphate* causes degeneration of the lower motor neurons with secondary chronic flaccid paralysis (*ginger or jake paralysis*)

The available statistics indicate that abstainers on the whole live longer than chronic alcoholics The fact that some chronic alcoholics may reach a ripe old age does not invalidate such a conclusion The Medical Research Council of Great Britain in a report published in 1923 concluded that the temperate consumption of alcoholic liquor may be considered to be physiologically harmless in the case of the large majority of normal adults that it is certainly true that alcoholic beverages are in *no way necessary for healthy life* that they are harmful or dangerous if 'certain precautions are not observed and that they are definitely injurious for most persons of unstable nervous system

Morbid Anatomy —The structural changes found on postmortem examination of chronic alcoholics are not specific or even characteristic They depend primarily on a high caloric intake Fatty infiltration or degeneration is observed in several organs particularly in the liver The heart may contain a considerable amount of fat over the epicardium Fatty infiltration and degeneration of the cardiac fibers may also occur There are no changes in the vessels which can be related to alcohol nor any evidence to indicate that the chronic use of alcohol causes arteriosclerosis The liver is usually enlarged and its at times remarkable increase in weight is due primarily to fatty infiltration and degeneration of the cells In some instances cirrhosis is superimposed The relationship between the chronic use of alcohol and advanced portal cirrhosis is not clear but it is certainly not a simple direct relationship Cirrhosis of the liver may be in some way related to certain types of nutritional deficiencies and to disturbances of intermediary metabolism The spleen too may show varying degrees of fibrosis depending on the amount of hepatic cirrhosis present In rare instances fibrosis of the pancreas or various grades of pancreatitis occur An atrophic type of gastritis is frequently encountered

The principal functional damage from the chronic use of alcohol is to the nervous system The mechanism of this effect is not clear It is not known whether the changes are due to an increase of fatty substances or to a lack of essential substances in the diet of chronic alcoholics Chronic leptomeningitis is frequently present as manifested by localized opaque and edematous areas When the edema is pronounced the condition is called wet brain or pia arachnoid edema These changes occur however in other diseases also Subdural hemorrhage (Virchow s pachymeningitis interna hemorrhagica) may result from trauma but seldom occurs spontaneously Presence of vitamin C deficiency may increase the tendency to traumatic subdural hemorrhage The *brain itself may be normal If it is* considerably reduced in size this is due to complicating arteriosclerosis or neurosyphilis Degenerative changes in the optic and peripheral nerves are found in a small group The nature of this finding is not clear but it is probably not due to alcohol itself It may be the result of chronic deficiency of essential food substances and in some instances the simultaneous use of nicotine also may be a factor

Symptoms —The abnormal manifestations exhibited by a chronic alcoholic patient can not always be attributed to alcohol Emotional instability and psychopathic tenden

cies are often present even *before* the chronic use of alcohol is established It should be remembered also that as the habit frequently lasts during a lifetime, numerous affections and diseases will develop independently

Nervous symptoms are common The mental processes may become dull particularly if the patient is unable to consume the accustomed amount of alcohol Often there is irritability and frequent loss of temper with outbursts of emotion fluctuating between rage and remorse Judgment may become impaired There may be progressive loss of muscular power associated with tremor of the hands and tongue In these persons who are rather over than undernourished, dilatation of the capillaries with resultant dilatation of the venules of the face (telangiectasis) frequently occurs Anorexia is often present partly as a result of chronic gastritis partly because of vitamin deficiency The fact that a large proportion of the caloric requirement is supplied by alcohol also plays a role Eructation and gastric and intestinal atony are frequent complaints Some of the digestive complaints are referable to an enlarged or a cirrhotic liver The presence of arteriosclerosis cannot be attributed to chronic alcoholism Similarly no chronic disease of the kidney is caused by alcohol Some of the contaminants or constituents of alcoholic beverages on the other hand exert an irritating effect on the kidneys The heart is affected by the chronic use of alcohol only so far as the resulting obesity can be associated with fatty degeneration of the heart In addition chronic alcoholic patients frequently do not eat and hence they are apt to develop beriberi heart nutritional edema pellagra and rarely scurvy

Chronic and excessive use of alcohol may undermine the constitution and lessen the resistance of the body to certain infections particularly to pneumonia The protective immunologic responses of the body seem to be impaired in chronic alcoholics but evidence is lacking that infectious diseases are more frequent in this group Whether chronic alcoholism exerts any specific unfavorable influence on the course of chronic tuberculosis is not definitely known

Diagnosis —When a history is available the diagnosis is not difficult In the absence of a history or if the condition is denied as is often the case particularly in female patients the manifestations may be puzzling Care should be exercised not to attribute all the symptoms of a chronic alcoholic to the use of alcohol As chronic alcoholism and luetic infection not infrequently coexist special study should be undertaken to rule out general paresis or other types of syphilitic involvement of the central nervous system

Prognosis —Permanent abstinence in chronic alcoholics is rare mainly because development of the habit depends on psychologic defects which in the course of prolonged use of alcohol become further accentuated

Treatment —No drug with specific benefit is known at present Successful treatment is possible only through proper analysis of the psychic difficulties of the sufferer In view of the fact that alcohol must not be consumed during such mental treatment and as most of the subjects are unreliable treatment should as far as possible be conducted in especially equipped institutions Sedatives and drugs with symptomatic benefit such as belladonna and amphetamine (benzedrine) may be used

The fundamental concept of the treatment of chronic alcoholism consists in attempts to improve the personal social or constitutional defects of the individual This can be achieved only through the cooperation of the patient Vacillations and doubts must be overcome by instillation of confidence and of convictions Past experiences and specific responses of the personality have to be taken into consideration Complete withdrawal of alcohol must be insisted upon Religious or other suggestive influences may be effectively utilized Cultivation of hobbies in chronic alcoholics may be helpful

Syndromes Related to Chronic Alcoholism —*Delirium Tremens* —This is an acute and usually transient psychosis observed often but not always after abstinence in persons chronically addicted to alcohol The condition does not develop in normal persons following acute intoxication Similarly it is not observed in chronic beer or wine drinkers In the history of patients suffering from delirium tremens heavy and often pro

longed debauch lack of food and sleeplessness frequently play a combined role Infections trauma and cardiac decompensation also may be precipitating factors The course is usually of two to ten days duration It is characterized by disorientation as to time and place by fear reactions the horrors' associated with visual or auditory hallucinations and by sensations of pain or paresthesias It is of interest that the content of these hallucinations may be the same in different attacks Visual hallucinations often take the form of small animals such as monkeys cats mice snakes or lice The onset may be gradual and the psychosis may be preceded by nervousness peevishness and restlessness Even during the active hallucination and disorientation the patient often retains his sensation of self and may enter actively into suggestions particularly in connection with the hallucinations Transitory rapport and mental clarity may appear Muttering and muscular tremor and incoordination are frequently present The delirium has many characteristics of an active vivid and changeable dream At times sudden fear reactions are accompanied by efforts to escape Paranoid trends may also dominate the clinical picture The delirium is usually worse at night The condition often clears up after a somewhat prolonged restful sleep Some of the manifestations of delirium tremens depend on the patient s fundamental make up and personality Persons with emotional difficulties are predisposed to delirium tremens Infectious diseases pneumonia in particular often precipitate the condition

The skin may be flushed or pale and is often covered with perspiration The pulse in young patients is high and bounding while in elderly subjects it is rapid and thready If the temperature is elevated it is of grave prognostic significance Albumin may be present in the urine Examination of the spinal fluid does not reveal any characteristic findings

PROGNOSIS —This depends on the severity of the reaction In cases with frank hallucinations the mortality rate is between 5 and 15 per cent Pneumonia and circulatory collapse are the usual immediate causes of death Fatal circulatory collapse can develop with unexpected rapidity

TREATMENT —No therapeutic measure is known at present to have a specific effect in delirium tremens The two most helpful measures consist in sedation and in proper feedings with concentrated food and with vitamin concentrates Large doses of sedatives and hypnotics should be given only under careful supervision as unexpected cumulative depression of the central nervous system and pulmonary edema frequently develop The patient should be kept in a comfortable position and should be disturbed as little as possible Oral or intravenous administration of 2 to 4 drachms of paraldehyde or of 10 to 30 grains (0 75–2 Gm) of chloral hydrate twice a day is frequently effective In milder cases 15 grains (1 Gm) of bromide three times daily may be helpful Barbiturates such as luminal in doses of 5 to 10 grains (0.3–0 75 Gm) are useful at times Frequently however the barbiturates accentuate the mental confusion Rarely hyoscine in doses of $\frac{1}{120}$ to $\frac{1}{60}$ grain (0.5–1 mg) may have a quieting effect Opium or its derivatives should be used with care Apomorphine is of doubtful value and may be harmful Strychnine is justified only as a measure in circulatory collapse It is given in subcutaneous doses of $\frac{1}{60}$ to $\frac{1}{30}$ grain (1–2 mg) In mildly delirious patients hydrotherapy may be effective Removal of adequate amounts of spinal fluid by lumbar puncture is at times useful

The water intake should be moderate, and part of this may be given in strong meat soups Concentrated foods with vitamin extracts administered every two or three hours also may be useful Nicotinic acid (or sodium nicotinate) in intramuscular doses of $\frac{1}{6}$ grain (10 mg) three times daily may clear up certain types of spastic muscular manifestations associated at times with delirium tremens If circulatory collapse is present this should be treated specifically

Korsakoff s Psychosis—This type of psychosis usually starts with delirium There is loss of memory but not of consciousness Frequently there is confabulation involving journeys or seeing certain persons The fabrication may appear reasonable and plausible at first The patient seems to feel constrained to yield to any suggestion made to him and to follow it with confabulation when fact fails The mental picture presented

by this condition may closely imitate that of delirium tremens Associated with the psychosis there are manifestations of polyneuritis and at times pellagroid skin lesions It is probable that in the etiology of this condition, just as in alcoholic polyneuritis nutritional deficiency particularly chronic deficiency of vitamin B plays a role

The TREATMENT is essentially the same as that of patients with delirium tremens but the prognosis is more serious Proper dietary measures are of particular importance Vitamin B concentrates or crystalline vitamin B_1 (thiamin) should be administered both orally and parenterally Parenteral administration of crystalline vitamin B_1 (20–40 mg) three times daily is indicated because intestinal permeability may be impaired Furthermore it improves the patient s appetite and makes possible subsequent effective oral feeding The use of nicotinic acid may be tried

Other Mental Manifestations—Chronic alcoholism may cause several additional types of mental disturbances particularly in individuals who have continued their drinking habits since early adult life The rate of incidence and the manifestations of these mental diseases depend primarily on the extent of the use of alcoholic beverages but they are also influenced by other factors In the United States the rate is higher among the foreign born than among the native population The nature of the acute mental manifestations seems to a certain extent to be determined by the innate personality of the patient Frequently the mental and neurologic syndromes overlap and a clear cut separation is impossible

Acute or Chronic Hallucinosis—In this condition hallucinations are mainly auditory in character The sensorium may be clear An *acute paranoid reaction* also occurs These patients become suspicious They develop jealous trends or persecutory ideas This reaction may be merely an accentuation of a 'normal submerged paranoid personality Some difficulty may be encountered in differentiating acute paranoid reaction from dementia praecox

Wet Brain—Chronic alcoholic patients often after several attacks of delirium tremens may suddenly fall into a semicomatose state associated with quiet muttering and delirium Their facial expression becomes fixed and staring Their tremulous hands make purposeless motions, grasping for objects or picking the bedclothes In contrast to delirium tremens this condition may run a prolonged course though sudden death due to circulatory collapse is not infrequent If recovery occurs this is rather slow and unless forced feeding is undertaken a marked degree of emaciation may develop

TREATMENT *consists mainly in careful* nursing taking precautions to avoid aspiration pneumonia and in adequate feeding Forced feeding through a nasal tube may have to be instituted Dehydration should be prevented by the administration of fluids through the channels indicated

Alcoholic Deterioration—This is a slowly developing change of the personality Patients suffering from this condition frequently maintain a fairly good insight They are rather carefree irresponsible and jovial Often they are easily influenced and their activities lead to conflicts with the social and moral codes Their capacity to do physical work becomes seriously impaired

Neuritis—This condition was described classically in 1822 by James Jackson Sr It is probably due to a vitamin B deficiency rather than to excessive use of alcohol but the latter plays more than an indirect role It occurs among steady drinkers The onset depending on the intensity of the drinking may be gradual with annoying paresthesias of the hands and feet or it may be rapid with motor manifestations Motor paralysis is apt to involve the feet legs hands and arms but not necessarily symmetrically The extensors of the feet are frequently affected and their involvement may last longer than that of other muscles giving a characteristic steppage gait In some instances difficulty may develop in the function of the sphincters of the bladder and rectum indicating cord involvement The complaints are at times due entirely to sensory disturbances as manifested by persistent severe pain or burning sensation Tachycardia is a frequent manifestation (*vagus neuritis*) Mental symptoms with hallucinations may complicate the picture (*Korsakoff s psychosis*)

The clinical characteristics and the eti

ology of this type of polyneuritis are quite similar to if not identical with those occurring in beriberi not associated with the use of alcohol The condition may persist for weeks or months but under proper treatment it ultimately clears up Not infrequently the clinical picture of polyneuritis is complicated by manifestations of *pellagra* including glossitis achlorhydria and diarrhea Some of the patients exhibit *nutritional edema* and cardiac decompensation (*beriberi heart*) with normal sized or with enlarged heart *Optic* and *retrobulbar neuritis* may develop without peripheral neuritis This lesion is usually attributed to methyl alcohol but its etiology is the same as that of alcoholic polyneuritis Nicotine may be a contributory factor

TREATMENT consists in withdrawal of alcohol and administration of a highly nutritional diet particularly rich in vitamins Vitamin B concentrates should be given by mouth and parenterally Of crystalline vitamin B_1 (thiamin) doses of 100 mg or more may be administered intramuscularly or intravenously every day Liver extracts are particularly beneficial if lesions of pellagra are present Massage of the extremities and physiotherapy should be given Smoking should be eliminated

SOMA WEISS

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METHYL (WOOD) ALCOHOL POISONING

Definition and Etiology—This intoxication is usually caused by the use of adulterated beverages containing methyl alcohol Accidental and industrial poisoning also occurs Methyl alcohol may be absorbed through the skin after a local application or poisoning may result from inhalation Methyl alcohol is somewhat more toxic than ethyl alcohol It is less readily oxidized and if its oxidation is incomplete formic acid is produced which may be responsible for acidosis A large percentage of methyl alcohol is eliminated in the urine Its chronic use is particularly harmful

Symptoms—Gastro-intestinal disturbances such as epigastric or abdominal pain nausea and vomiting and obstinate constipation may indicate the onset of intoxication Weakness dizziness vertigo and headaches may precede delirium coma and unconsciousness Nystagmus dilated pupils dyspnea and cyanosis are also frequent features The dyspnea may be severe and associated with intense thirst The coma is considerably more prolonged than that following an equal dose of ethyl alcohol The estimated fatal dose is between 100 and 250 cc but marked variations in individual susceptibility exist Death may occur suddenly either soon after the intoxication or following several days of coma Repeated ingestion of methyl alcohol leads to lassitude mental deterioration and delirium

One of the dreaded neurologic effects is *optic neuritis* This is usually bilateral It may start with dimness of vision and scotoma and may progress slowly or rapidly to complete blindness Blindness may develop within a few days Some improvement may occur subsequently

Treatment—This should consist in effective measures for the elimination of methyl alcohol Gastric lavage should be performed at once and 1 ounce of Epsom salts should be left in the stomach Lavage of the colon should be performed three times a day Dehydration should be prevented and circulatory collapse should be treated by appropriate measures

SOMA WEISS

BARBITURATE INTOXICATON

The barbituric acid derivatives are by far the most widely used sedatives and hypnotics Accidental and unintentional intoxication with barbiturates has become common and suicides are frequently committed with these drugs Their widespread use is due partly to their frequent prescription by physicians but also to the fact that they can be freely purchased without a medical

order If morphine and cocaine addicts are unable to procure the drugs to which they are addicted they often resort to the use of large doses of barbiturates Since the introduction of barbital into clinical medicine, a long series of barbituric acid derivatives have appeared under various trade names The action of all the members of the group is quite similar, the most essential difference being in the duration of effect Allonal, amytal barbital dial evipal gardenal ipral luminal medinal nembutal noctal pentobarbital pernocton phenobarbital and veronal are some of the more frequently used members of the barbiturate group of hypnotics

Acute Intoxication—This may be the result of individual susceptibility to a therapeutic dose or may occur following accidental or intentional consumption of a large amount of the drug Persons in depressed nervous states are susceptible to the barbiturates

Physiology—The barbiturates are taken up rather diffusely by all parts of the brain as well as by tissues of other organs The effects depend primarily on their action on the brain stem This does not however indicate that the vegetative centers of the brain stem combine with a relatively large amount of barbiturates but rather that the functions of the midbrain centers are particularly susceptible to the chemical action of these drugs There are no detectable structural changes in the central nervous system following acute poisoning

Symptoms—These vary with the amount of the drug taken as well as with the channel of administration When absorption is gradual confusion a dull sensation in the head and ataxia may be the first manifestations Subsequently impairment of the sense of smell and of taste and difficulty in swallowing occur Nausea vomiting generalized excitement and hallucinations may precede the onset of sleep This sensory or motor excitement varies with different barbiturates In the early stage of sleep the respiration is of the Cheyne-Stokes type subsequently it becomes rapid and regular The heart rate and blood pressure remain essentially unaltered in the early stage Subsequently circulatory collapse is apt to appear Cyanosis moist skin and the appearance of congestive rales over dependent portions of the lungs are grave signs The pupillary and deep reflexes are usually maintained for a relatively long time in coma but the presence of Babinski and abdominal reflex responses indicates disturbances in the function of the pyramidal tracts Death may be caused by direct paralysis of the respiratory center but more frequently it is due to vasomotor collapse and secondary bronchopneumonia

Diagnosis—The presence of coma with quiet regular respiration in subjects in whom drug intoxication is suspected should raise the possibility of barbiturate poisoning A definite diagnosis can be established only with the aid of a proper history and of chemical tests

Prognosis—The course of barbiturate poisoning is treacherous Death may occur even several days after the ingestion of the drug Pneumonia may prove fatal after the patient has recovered from the immediate effects of poisoning

Treatment—If the intoxication is mild withdrawal of the drug relieves the patient In cases of severe intoxication gastric lavage should be performed promptly with a warm solution of permanganate or warm saline solution Before the removal of the tube from 30 to 60 Gm (1–2 ounces) of magnesium sulfate in 50 per cent solution should be instilled into the stomach Strychnine in doses of 5 mg (1/12 grain) or more may be given intramuscularly or intravenously every two hours The dose should be reduced as the general condition of the patient improves Picrotoxine in doses of 0 5 to 1 mg (1/120–1/60 grain) administered intramuscularly every two to six hours depending on the condition of the patient is an effective remedy Ephedrine in amounts of from 20 to 30 mg (1/3–1/2 grain) or benzedrine in doses of from 10 to 15 mg (1/6–1/4 grain) at two hour intervals may be useful in arousing the patient If cyanosis and respiratory disturbances are present inhalation of a mixture of 5 or 10 per cent carbon dioxide and 95 or 90 per cent oxygen is indicated Coramine may give temporary relief but if the respiration does not show a tendency to improve a respirator should be used

Chronic Intoxication ("Barbiturism")—This is quite a frequent occurrence It plays a more important role in medicine to

day than cocainism although it bears quite a different significance Barbiturism develops as the result of prolonged and careless use of these hypnotics through medical prescription or as a household remedy Not infrequently it occurs among drug addicts who have resorted to barbiturates as a substitute for morphine heroin or cocaine Barbiturism is not associated with withdrawal symptoms Tolerance is not formed

Physiology—The effect of the chronic use of these drugs depends on chronic intoxication of the nervous system and depression of vegetative functions Degenerative changes in the nerve cells have been observed in animals following prolonged administration of the barbiturates

Symptoms—Gradual loss of ambition impairment of capacity for concentration and an increasing desire to sleep particularly after meals are the most common manifestations Vertigo ataxia, nystagmus visual hallucinations difficulty with accommodation and with the function of ocular muscles squint thick or anarthrous speech ataxia or paralysis of the limbs may develop Failing of memory with slowness of thought is sometimes experienced Changes in the reflexes either suppression or accentuation and the appearance of pyramidal signs may further complicate the puzzling clinical picture Albumin and casts may appear in the urine and hematoporphyrinuria is a rare complication

Diagnosis—Chronic barbiturate poisoning presents a variable and often puzzling clinical picture and the diagnosis may be exceedingly difficult if a history is not available The manifestations may imitate those of encephalitis lethargica acute psychic depression pseudobulbar palsy general paresis or delirium tremens

Prognosis—This is usually favorable

Treatment—Chronic intoxication requires only the withdrawal of the drug If mental problems are present they should be managed with psychotherapeutic methods

SOMA WEISS

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OPIUM INTOXICATION

The clinical significance of opium intoxication depends on whether it occurs in its acute or its chronic form The taking of toxic doses with suicidal intent or accidentally in the course of medication is a common cause of acute intoxication The chronic opium addict who is in the tolerant state never suffers from acute opium poisoning but severe poisoning and even death frequently occurs among opium addicts who have lost tolerance to the drug by a few weeks of abstinence Followng a half hearted or forced cure many of these cases ignorantly take the size of dose to which they had been accustomed when tolerant but which is now poisonous to them

LAWRENCE KOLB

ACUTE OPIUM INTOXICATION

The symptoms of acute intoxication are essentially the same regardless of whether opium or one of its derivatives such as morphine dilaudid or heroin is the causative agent Flushing of the face giddiness lassitude and incoordination first occur drowsiness quickly follows the skin becomes pale respiration and pulse are slowed and the pupils contracted Nausea and vomiting may be early symptoms Following large doses somnolence rapidly deepens into sleep and coma from which the patient can be roused in the early stages As coma deepens he cannot be roused the reflexes disappear the temperature falls the pupils become pin point the pulse may become irregular and feeble and cyanosis develops Respirations are always depressed and may be reduced to a few gasps per minute Cheyne-Stokes type of respiration is common Asphyxial convulsions more common in infants may occur in the late stage Edema of the lungs is common in this stage but not necessarily fatal Dilatation of the pupils is of grave prognostic significance Recovery may occur in patients so severely poisoned that they are in deep coma and are breathing only two or three times per minute The combination of cyanosis dilated pupils and pulmonary edema is always fatal Patients with pulmonary edema may awaken from coma show improved respiration and then die four or five

hours later, *apparently from progressive* weakness of the heart and the edema In recovery the pulse gradually improves and the coma changes to a prolonged deep sleep which may last for several hours or even a day or two Headache mental depression vomiting itching of the skin and difficulty in initiating micturition follow intoxication This latter symptom may also be present during the more acute stages of intoxication, and calls for attention and treatment Some persons may develop maniacal excitement and, on rare occasions convulsions following the medicinal use of morphine or codeine and patients with severe anemia and hepatic *insufficiency are thought to be particularly* susceptible to the depressant action of morphine Infants are highly susceptible to opiates Myxedematous patients may be put into deep coma by ¼ grain (0 016 Gm) of morphine

Diagnosis—The history of the medicinal or other use of narcotics together with the clinical picture is usually sufficient to establish the diagnosis Pin point pupils though not specific for opium poisoning help to differentiate the condition from alcoholic coma The gradual development of coma together with the depression of respiration as low as eight or ten per minute, is highly suggestive of opium poisoning In doubtful cases an examination of the urine may disclose the presence of morphine

Treatment—Treatment consists in efforts to remove the drug from the gastro intestinal tract if the opium has been taken by mouth to stimulate respiration and to prevent circulatory collapse Gastric lavage should be performed promptly with several liters of potassium permanganate (1 to 5000) Lavage should be performed through a nasal tube as lavage by the ordinary stomach tube increases the tendency to coma and to edema of the lungs The best chemical antidote is charcoal After lavage 50 cc of 20 per cent charcoal suspension should be *introduced* together with 50 cc of 50 per cent magnesium sulfate solution Repeated gastric lavage for the removal of morphine excreted in the stomach is of doubtful value and may be harmful Edema and bronchopneumonia have been produced by it The patient should be covered warmly He should be kept awake by reflex stimulation such as the inhalation of ammonia in the form of smelling salts and cold ablutions to the skin Walking the patient around to keep him awake is probably harmful in view of fatigue The greatest danger is from respiratory collapse Hot strong coffee and small doses of caffeine are good respiratory stimulants The administration of 10 per cent carbon dioxide and 90 per cent oxygen is also effective The patient may have to be placed in a respirator Coramine and metrazol are the best respiratory stimulants, and of these two coramine is preferable as it is less likely to cause convulsions in persons poisoned by opium To a patient in coma *5 cc of 25 per cent solution of coramine* should be given intravenously A deeply comatose patient breathing only a few times per minute may be awakened and the respiration greatly improved by this treatment, but in serious cases the treatment has to be repeated several times at intervals of a few minutes If drowsiness sets in again after a few hours a new injection may be given intramuscularly Failure of the heart evidenced by tachycardia and wheezing of the lungs should be combated by the intravenous administration of digitalis If great restlessness or convulsions occur from the use of coramine 15 grains (1 Gm) of chloral hydrate in solution should be given by rectum A common effect of severe opium poisoning is bronchopneumonia Sodium sulfadiazine 1 Gm dissolved in 20 cc of water administered every four hours intravenously until the patient can swallow, is said to be an effective preventive Sulfadiazine should be continued for twenty four hours after the subsidence of the coma

LAWRENCE KOLB

CHRONIC OPIUM INTOXICATION (OPIUM ADDICTION)

Opium addiction is a physiologic condition of tolerance to and dependence upon opium brought about by the continued use of some drug of the opium series usually in increasing doses Tolerance may be built up to increasing doses of many drugs but opium is the only drug that produces dependence Dependence is the most striking characteristic of addiction and is what most people have in mind when they speak of opium addic

tion but the most potent causes of continued chronic addiction to opium are psychologic The habitual user of morphine the most important opium derivative can in about nine months build up a tolerance to 60 grains (4 Gm) per day an amount sufficient to kill or seriously poison about fifteen unaddicted adults but instead of being killed or seriously harmed by this large dose the addict suffers intensely and may even die in collapse if it is abruptly taken from him

The limit of tolerance is not known Addicts have been known to take an ounce of morphine in a week and experimentally a strongly habituated morphine addict has been given 20 grains (1.3 Gm) of morphine sulfate intravenously within an hour with only mild discomfort and no signs whatever of collapse

With unrestricted access to the drug the average addict will take about 15 grains (1 Gm)of morphine daily Doses vary with the degree of normality of the individual Normal people tend to stabilize the dose while psychopaths are prone to increase it A few nervously normal individuals get along on a grain or two a day while the extreme psychopaths may require from 30 to 60 grains (2 to 4 Gm) to satisfy their craving Because of the scarcity of opiates in the illegitimate market at the present time the average daily dose of addicts who are supplied by *narcotic peddlers is probably not* more than 1 or 2 grains (0 06 to 0 13 Gm) of morphine This may be fraudulently diluted so that the product that he actually buys contains as little as 5 or 10 per cent of morphine

Under the influence of necessity or for experimental purposes addicts shift from one opiate to another with only a slight feeling that something is different However adjustment is made in a week or two The morphine addict who shifts to heroin does not reduce the daily dose He apparently requires at least an equal amount of heroin to satisfy the physical dependence built up by morphine

Any preparation of opium that relieves pain will bring about physical addiction in anyone who uses it continuously in increasing doses but addiction to codeine is extremely rare apparently because codeine does not produce euphoria

In the Orient eating and smoking opium are methods of choice among addicts but the alkaloids have been introduced in recent years and their use is growing In the United States the use of such preparations as laudanum and powered opium was once fairly common among addicts, but at the present time the concentrated preparations such as morphine heroin and dilaudid are used almost exclusively except among the Chinese residents who still persist in smoking The alkaloids are usually taken hypodermically or intravenously Heroin was at one time used extensively by snuffing but the product now available in the illegal market is diluted too much to be effective as a snuff

Smoking is the least harmful form of addiction The hypodermic or intravenous administration of the alkaloids is the most harmful A reason for this is that addicts who use the alkaloids this way quickly build up tolerance to large doses Most addicts in the United States use morphine hypodermically A large proportion of the psychopathic group inject morphine or heroin intravenously Such weak preparations as paregoric may be taken by mouth when the alkaloids are not available

Etiology.—The cause of addiction depends in a measure upon the setting in which it occurs From the standpoint of origin addicts may be divided into two classes (1) Pure dissipators and (2) those whose addiction resulted from medication The dissipators accidentally find that opiates have an agreeable effect upon them and become addicted through their quest of this effect In medical cases the patients become addicted through the prescribing of physicians or by self medication for some disease for which an opiate is apparently indicated Addicts may be further divided into the nervously normal and the nervously abnormal Among the latter are many who were introduced to the drug through medication The nervously abnormal group comprises persons suffering from various forms of deviated personalities including psychopathic psychoneurotic and psychotic individuals and persons with inebriate personalities Opiates are used by these various abnormal groups as a method of solving their problems The narcotizing effect of these drugs is for them a more or less satisfactory form

of adjustment of which they have accidentally become aware The nervous pathology of these types whether due to heredity or environment or to both is by far the most important cause of their continued addiction These unstable individuals whether originally addicted through dissipation or by medical means have feelings of inferiority restlessness and discontent which under the influence of opiates, are replaced by confidence calmness and contentment The degree of contrast with their usual selves is in direct proportion to their deviation from the normal It amounts to intense pleasure in some psychopathic cases, but it wanes as tolerance is established and is finally lost altogether Efforts to recapture that pleasure in the original form account for the enormous doses that some addicts build up to and memory of it is a potent cause for their relapse after cure

Individuals comprising the normal group usually get well promptly when the reason for the medication is removed hence such individuals are rare among chronic addicts A study made in 1925 showed that 14 per cent of chronic addicts belonged to this class A study made at the Public Health Service Hospital at Lexington Ky in 1938 showed that only 3 8 per cent of the addicts there had normal nervous constitutions Among the abnormal group are a large number of carefree individuals devoted to pleasure seeking new excitements and sensations and usually having some ill defined instability of personality that often expresses itself in mild infractions of social customs These mildly psychopathic individuals make up the largest percentage of addicts There is a smaller group of more abnormal psychopaths and a still smaller group of psychotics The inebriates comprised approximately 21 5 per cent of two large groups of addicts that have been carefully studied Addicts of the inebriate type are probably closely related to the psychoneurotics A distinguishing feature is that they have a periodic impulse to drink and usually become addicted to opiates through taking them in the form of morphine to sober up from the sprees After cure members of the inebriate group have a strong tendency to relapse by the alcohol route They take alcohol in order to satisfy an indefinite craving characteristic of them and when inhibited by it they recklessly take morphine again Some acquire a questionable cure of the morphine habit by becoming chronic alcoholics There are a few psychotic addicts but opium plays only a very minor causative role if any in these cases On the contrary, it is probable that the habitual use of it by easing stresses in predisposed individuals saves some from breaking down into frank psychosis

Morbid Anatomy—The chronic opium addict is usually a pale anemic malnourished individual The arms shoulders buttocks legs and even the trunk of many of them are covered by scars of old abscesses produced by the use of dirty needles Similar scars may result from abscesses due to the injection of cocaine but the cocaine addict who reaches the abscess stage is practically always also a morphine addict Other than the abscess scars there is no proved morbid anatomy due to chronic opium intoxication Degenerative changes in the brain spinal cord heart liver and kidneys have been reported in association with it but in all probability these changes have been due to associated diseases malnutrition or vitamin deficiency so common among addicts

Physiologic and Psychologic Effects.—Minor physiologic changes occur in the course of opium addiction These changes are apparently associated with the adjustment incident to tolerance The mechanism of tolerance is not understood Among the recorded changes is a tendency to a low red cell count and a high leukocyte count The blood cholesterol is usually increased The lactic acid is uniformly high and the specific gravity of the blood is lower than normal The brain potentials show an increased alpha output in sustained addiction

After a few weeks of abstinence from opiates patients appear to have recovered physically but there is not complete readjustment of all physiologic processes for several months The basal metabolic rate and the level of inorganic phosphorus in the blood are subnormal as late as the sixth month after the last dose is taken The libido is markedly reduced or abolished in men and the menses in women by large doses (15 to 30 grains [1 to 2 Gm] of morphine daily) Both promptly return on withdrawal of the drug Sterility never results

The death rate among addicts is much higher than in the general population This is in part due to the fact that a large proportion of addicts are already diseased when they contract the habit The difficulties that they have in maintaining addiction in a hostile environment is also important They are alternately sick from forced abstinence and lethargic from eager overindulgence when the needed drug is obtained General vitality is therefore lowered and is often still further decreased by malnutrition Abscesses and tetanus contracted by the use of soiled needles and malaria and syphilis from the use of common needles passed from addict to addict add to the toll

The effect of opiate addiction on personality and character is confused Much of what is regarded as evidence of moral deterioration is really original psychopathology plus difficulties placed in the way of the individual by society Many drunkards who become opium addicts are improved morally physically and socially by the change Some shrinking individuals are made more efficient by small doses of opiates that tend to blot out their sense of inferiority Nevertheless continued addiction has some deleterious effects on character The secrecy of the habit the practice of evading issues and of solving difficulties by blotting them out through the use of narcotics the parasitic lives that so many addicts are compelled to live the conflict with the law, the poverty and malnutrition that result from the spending of so much money to secure needed narcotics in the illegitimate market tend to bring about physical and moral deterioration but intelligence is not impaired and psychoses do not occur except rarely as acute episodes on withdrawal of the drug from highly susceptible individuals Character deterioration is greater in opium addicts who were much below par in the beginning than in those who had social responses and habits approaching normal The chief crime committed by opium addicts is violation of narcotic laws Many rob and steal to get the drug and some indulge in confidence games Because of the soothing effect of all addicting opiates violent crime among addicts is rare The nervously normal addict who regularly secures a sufficient supply of drug for his physical needs shows no deterioration in morals or in social and intellectual activities An 81 year-old normal mother of six healthy children took 3 grains (0 2 Gm) of morphine daily for 65 years Similar instances are not uncommon

Children born of addicted mothers are as a rule healthy but in cases where 20 or 30 grains (1.3 to 2 Gm) of morphine per day have been taken the newly born infant may show withdrawal symptoms which need treatment

Withdrawal Symptoms (Abstinence Syndrome) —The withdrawal of opiates from persons habituated to their use is followed by a train of severe symptoms The intensity depends upon the duration of the addiction the size of the accustomed dose and the rapidity of the withdrawal These symptoms are dreaded by addicts Added to the immediate discomfort is the fear of death that some of them have during the most intense phase of withdrawal The symptoms represent the 'running wild of functions that had learned to operate normally under the tremendous check that opium had put on the nervous system It is as if the fly wheel had been removed from an engine and some patients describe the situation by saying that they feel as if they would fly to pieces

The drug is missed always about eight hours after the last dose Restlessness and a feeling of nervousness then occur From then on there is a gradual development of symptoms with yawning lacrimation rhinorrhea perspiration goose flesh hot flashes chills loss of appetite mydriasis tremors and twitching of muscles Insomnia may be distressing Vomiting and diarrhea may be so severe as to dehydrate the patient and cause considerable loss of weight Pains in the abdomen and legs are common

Measurable signs that invariably occur are increased respiratory rate rise in temperature and blood pressure and increase in blood sugar and in the basal metabolic rate Wide dilatation of the pupils associated with thready pulse and irregular respiration is a danger sign Death presumably from circulatory collapse occasionally occurs Some patients become excited while others are depressed during withdrawal and mild psychotic episodes occur in rare cases The symptoms reach the maximum of se-

verity in about 48 hours and then gradually decline About four or five days after the last dose of morphine the patient feels reasonably comfortable and in two weeks there are no striking physical symptoms except insomnia which may distress him for several months The recovery in young men is rapid After two weeks they may feel nothing of a distressing nature except insomnia Addicts past fifty may feel lethargic and depressed for two months or more

Diagnosis—Diagnosis presents no difficulty as a rule because the average patient readily admits his addiction The underworld type of patient is usually pale owing to anemia and many of them have characteristic cutaneous scars due to needle abscesses or dark lines along the course of veins that have been used for injections Addicts who have been able to sustain themselves with sufficient food and who are clean in their habits may show absolutely nothing with the possible exception of a fresh needle mark at the point of a recent injection The pupils are normal during sustained addiction Isolation brings out withdrawal symptoms together with an admission that what is needed is an opiate Morphine can be detected in the urine for about four days after the last dose has been taken and in doubtful cases an examination of the urine may clear up the diagnosis

Treatment—The treatment of a case of drug addiction in a person with a normal nervous constitution and no painful physical disease presents no great difficulty Persons with abnormal personalities or with physical disease present more serious problems because they are prone to change their minds about the necessity of treatment before withdrawal is completed and are very prone to relapse shortly afterwards There is no specific remedy for the treatment of withdrawal symptoms The essential thing is to deprive the patient of the drug as painlessly and as harmlessly as possible Many empirical methods for doing this have been devised Some of them are harmful and have contributed to the death of patients in withdrawal Treatment with large doses of toxic drugs and extreme purgation should be especially avoided Abrupt withdrawal is one of the least harmful of the objectionable methods It is widely used in prisons and is effective, but it leaves psychologic scars that contribute to relapse Abrupt withdrawal combined with a few doses of codeine may be used without harmful effects physical or psychologic, in patients who have a very mild addiction

Treatment can be carried on at home and many addicts, even of the relapsing type have successfully carried themselves through the withdrawal period at home without the help of a physician, but the management of an addict at home is usually not satisfactory Preferably treatment should be carried on in a hospital in which the environment can be controlled The approach to the patient should be made, however, with an eye to his psychologic adjustment, because this is most important for continued cure The patient should be stabilized on from 1 to 4 grains (0 016 to 0 06 Gm) of morphine daily in four equally divided doses depending upon the degree of his addiction for two to four days before withdrawal is attempted Withdrawal should then be made rapidly in accordance with a fixed schedule of opiate medication It should be effected in from four to ten days, depending upon the severity of the addiction and the physical condition of the patient

The schedule has to be varied with the patient but temporizing with him by the administration of morphine beyond the scheduled period or in increased amounts is seldom justified A good schedule is as follows For a patient who has been stabilized on 4 grains (0 26 Gm) of morphine daily give 1/4 grain (0 016 Gm) of morphine four times per day on the first day Give 1/8 grain (0 008 Gm) of morphine four times per day on the second day and two 1/8 grain (0 008 Gm) doses at twelve-hour intervals on the third day After this codeine should be substituted for morphine on a similar schedule for three days longer Give 15 grains (1 Gm) of bromide three times per day beginning on the second day to reduce intense nervousness and restlessness Larger doses of bromide up to 60 grains (4 Gm) three times per day may be given but in no case should administration be continued more than three days because of the danger of bromide intoxication

The insomnia responds better to paraldehyde than to other

turates especially have been found to cause confusion and delirium and to increase restlessness in some addicts undergoing withdrawal After a low cleansing enema 10 to 15 cc of paraldehyde in warm olive or cotton seed oil should be given by rectum before bedtime for several days beginning on the second day of treatment Diarrhea may be troublesome for the first two or three days It should be controlled when necessary by 15 grains (1 Gm) of bismuth subcarbonate three times daily If at the beginning of treatment the patient is constipated an enema should be given Two ten minute flow baths per day should be given during the period of actual withdrawal to reduce restlessness and relieve aches and pains in the legs and back The temperature of the water should be gradually increased from 98° to 104° F (36 7° to 40° C) and the patient should be carefully watched for rapid pulse and complaints of faintness If these occur he should be promptly removed from the bath Aspirin 5 grains (0.3 Gm) every two or three hours reduces the intensity of aches and pains Intravenous infusions reduce restlessness and restore fluid and salt loss One thousand cc of 0 85 per cent NaCl or Ringer s solution should be given in the morning and 1000 cc of 5 per cent aqueous solution of dextrose in the evening

The patient should be encouraged to eat during the entire withdrawal period He may not be able to tolerate anything except liquids such as eggnog milk and fruit juices during the first two or three days however It is not necessary or desirable to keep him in bed against his will He should stay in the hospital under supervision for at least two or three weeks and preferably for several months after withdrawal Sedatives and hypnotics should be used sparingly if at all during this period As a rule they should be discontinued two or three days after the actual withdrawal of the opiate The addict who leaves the hospital with advice to take such drugs usually overdoses himself with them and quickly relapses to the original opiate

When possible psychotherapy and constructive work preferably out of doors should be continued for two or three months after the actual withdrawal This treatment by ventilating the patient s original difficulties, building him up physically and establishing new habit patterns tends to give him a new outlook on life and fortify him against relapse

Relapse is common in any event in the nervously unstable and in persons suffering with such physical conditions as asthma migraine and neuritis Among the unstable the fundamental cause is identical with that which led them into the original addiction Physical disease seductive memory of past pleasant experiences with narcotics conditioned memory association indulgence in alcohol and a hostile environment contribute to it As with the chronic alcoholics many relapses may eventually be followed by permanent cure

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COCAINE INTOXICATION

(*Acute Intoxication*)

Acute cocaine poisoning is fairly common It occurs as a rule in persons in whom the drug is used as a local anesthetic Poisoning

from throat and nasal sprays in which co caine was used was once common Unlike opium addiction a rare case of acute cocaine poisoning may occur in an active cocaine ad dict Accidents are due to excessive doses mistakenly given or to faulty technic Susceptibility to the drug varies greatly owing to individual idiosyncrasies and dif ferences in the rate of absorption The addi tion of epinephrine to cocaine injections reduces the toxicity and increases the an esthetic effect chiefly by delaying absorp tion but epinephrine makes some hyper sensitive individuals more susceptible to cocaine collapse Death has resulted from ⅓ grain (0 02 Gm) of cocaine and serious poi soning has occurred from much smaller doses The danger is much greater when con centrated solutions are used Less dangerous drugs have largely superseded the use of cocaine as a local anesthetic

Symptoms—The symptoms in cocaine poisoning are similar to those due to the syn thetic substitutes procaine butyn and so on In mild intoxication resulting from slow absorption or small doses there may be ex-citement pleasurable or disagreeable the pa-tient is restless more garrulous than normal, and often anxious and confused Along with these symptoms there may be laughter ver tigo rapid pulse and irregular respiration *Larger doses cause a feeling of faintness to* gether with pallor sweating rise of tempera ture dilated pupils dyspnea, Cheyne Stokes respiration tremors and mild convulsive twitchings that may go on to tonic or clonic convulsions Death may occur from cessation of respiration during a convulsion In most of the fatal cases convulsions are absent but collapse quickly occurs apparently from rapid absorption If the patient lives a few minutes after the toxic dose has been taken he almost always recovers

Treatment—Treatment should begin with *prevention Careful attention to the* preparation and dosage guards against errors that have caused many deaths If idiosyncrasy is feared the previous admin istration of a barbiturate adds a margin of safety by suppressing convulsions and pre-venting their interference with respiration When an overdose has been taken the pa tient should be placed in the shock position If the drug was taken by mouth the stom ach should be emptied immediately Sodium luminal 5 to 10 grains (0 3 to 0 75 Gm) should be given intravenously to prevent or suppress convulsions as indicated Sodium amytal is also effective Artificial respiration should be instituted if necessary

LAWRENCE KOLB

CHRONIC COCAINE INTOXICATION

A mild form of chronic addiction to co caine has occurred for centuries among the Indians in the west of South America espe cially in Peru and Bolivia Many of the na tives believe that by chewing the coca leaves they will be able to do more physical work with less fatigue and without feeling the pangs of hunger and thirst Many of them use the drug regularly however and with reported deleterious effects on both physical and mental health In the United States cocaine addiction is now extremely rare and never has been common as a continuing ad diction There were only seven cases among 150 addicts studied in 1924 Among the first 3000 admissions to the United States Public Health Service Hospital at Lexington Ky which was opened in 1935 for the treatment of narcotic addicts there was only one case of cocainism Mixed cocaine opiate addiction *has been quite common* in the past but is also decreasing There was not one case of pure cocaine addiction in a series of 210 cases studied in 1927 but 35 per cent of the total number had been addicted to both cocaine and an opiate at one time or another A number of persons dissipate with cocaine now and then but never become *addicts* Their indulgence is comparable to week end drinking

Etiology—Instability of personality is of the same importance in the causation of chronic cocaine addiction as in opium addic tion but unlike opium addiction physical dependence is not a factor In cocaine addic-tion there are no distressing withdrawal symptoms The anesthetic properties of co caine were discovered in 1884 and from then until the Harrison Narcotic Law was en acted in 1914 the drug was widely used in this country in *sprays for* asthma hay fever and throat infections Many cases of addic tion resulted from this medicinal use of co

caine but the most common cause of addiction has been dissipation Use of the drug is begun out of curiosity and it is continued because of its pleasurable effects

Cocaine has served to introduce many addicts to a career of chronic opium addiction Psychopathic cases looking for thrills start with cocaine and increase their dose until the state of anxiety produced by it becomes distressing to them They then begin to use an opiate in order to lessen the disagreeable effects of the cocaine and for a time take both drugs The opiate finally becomes a necessity and cocaine is discontinued for economic reasons Some stop using it because of its obviously bad effects on their health and its tendency to produce emaciation and convulsions

Cocaine is taken by addicts as a snuff or by the hypodermic or intravenous route Snuffing often leads to ulceration or even perforation of the nasal septum

Tolerance to cocaine is built up in human beings but it is never as high as with opiates Animals are said to become more sensitive from continued use of the drug The average cocaine addict will take about 6 grains (0 4 Gm) of the drug per day Psychopathic subjects have been known to take 30 grains (2 0 Gm) per day but few can tolerate such large doses for long periods The simultaneous use of an opiate increases the tolerance to cocaine A cocaine and morphine addict has been known to take 60 grains (4 0 Gm) of cocaine daily along with the morphine *for several days Such large doses* quickly lead to disaster

Symptoms—The effects of small doses of cocaine in the beginning of addiction are pleasant There is a sense of well being exhilaration and optimism Confidence is increased and the libido is enhanced When the accustomed dose is not taken there is a decided let-down with feelings of languor and somnolence Increasing doses and continued use lead to loss of appetite digestive disturbances diarrhea emaciation insomnia peculiar sensations as of crawling under the skin and mild tremors Large doses always cause feelings of nervousness that pass over into anxiety and in addicts who take excessive amounts over long periods the anxiety gradually develops into persecutory delusions and any physical overactivity culminates in convulsions Doses of 20 to 30 grains (1.3 to 2 0 Gm) per day if persisted in will always lead to convulsions and a paranoid type of psychosis Recovery from such psychosis practically always occurs shortly after the drug is discontinued

As with opiates the pleasure derived from the use of cocaine depends on the degree of abnormality of the individual In normal people pleasurable sensations may be absent altogether and even in psychopaths the pleasure is accompanied by disagreeable sensations when large doses are taken The combined use of morphine or heroin with cocaine increases the pleasurable effects of cocaine by adding the element of sedation Some extreme psychopaths who use this combination have at times feelings bordering on ecstasy Deterioration is rapid with such cases Unlike opium cocaine directly increases the propensity of criminally inclined persons to violent crime By its stimulating effect on physical and mental processes the drug increases confidence and daring and makes the users more effective as criminals Paranoid delusions supply some individuals with motives

Morbid Anatomy—Emaciation is usually extreme Scars over the arms shoulders buttocks and legs similar to those found in morphine addicts are often present Some of the scars in the case of cocainism may be due to necrotic action Perforation of the nasal septum is found in some cases There is no other proved morbid anatomy As *with morphinism pathologic changes due to* associated malnutrition and vitamin deficiency may be present

Diagnosis—The history usually establishes the diagnosis Ulcerations of the nasal septum are often present Scars from abscesses and discoloration along the course of veins or fresh needle marks point to addiction but do not differentiate cocaine from opium addiction Laboratory tests are not helpful

Treatment—The drug should be withdrawn abruptly with only symptomatic treatment There are no painful or distressing withdrawal symptoms such as occur in morphinism and collapse never occurs When the drug is withdrawn the body processes that have learned to work normally under the powerful stimulant are depressed

for several days until functional readjustment occurs As a result the patient feels languid but not distressed Where the dose has been large sleep may last as long as thirty six hours In extreme cases it may be desirable to awaken the patient by a small dose of cocaine in order to give nourishment The languor may last for several days longer Appetite rapidly increases and body weight is quickly regained There is a strong desire for the drug for some time, but there is no craving comparable to that following opiate withdrawal The after treatment is similar to that for morphinism Relapses are frequent and are due mostly to personality defects The *prognosis* for combined opiate cocaine addiction is worse than that for single addiction to either drug for the reason that the mixed addict is as a rule more psychopathic

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FOOD POISONING

POISONING DUE TO LIVING BACTERIA OR BACTERIAL TOXINS CONTAMINATING FOOD

Definition —Under this heading we shall discuss only that type of poisoning due to the contamination of food with certain bacteria or bacterial toxins Botulism mushroom poisoning mussel poisoning and poisoning due to simple chemicals or allergens in food are discussed separately

The term ptomaine poisoning which is commonly applied by both physicians and laymen to an acute digestive upset of the type described here is misleading and improper because as will soon be shown the trouble is almost always due to living bacteria Actually it is a question whether there is such a substance as a ptomaine, and today no well informed person uses the word. Authorities insist that it should be abandoned, but it is difficult to overcome a habit of speech which has taken such firm hold of laymen newspaper writers, and even the rank and file of the medical profession.

Not only is the term itself inaccurate but worse yet, whenever a series of cases of reported food poisoning is carefully investigated it is found that frequently the diagnosis was wrong and the accused food was not responsible for the illness Thus, in one series of forty three fatal cases in which the reported diagnosis was ptomaine poisoning necropsy revealed in every instance some other cause of death such as appendicitis, ruptured ectopic pregnancy peritonitis tuberculosis meningitis encephalitis acute alcoholism carbon monoxide or metallic poisoning toxemia of pregnancy abortion malaria diphtheria fulminating poliomyelitis bacillary dysentery coronary disease pneumonia or cerebral apoplexy

Food may cause illness either because it contains living bacteria which after ingestion by the victim grow in the bowel or blood and produce toxins or because it contains toxins already formed by bacteria The toxins may be formed and retained in the bacteria, or they may be extruded by these bacteria or, conceivably they may be formed from the food through the action of the bacteria

Etiology —*Both in the* United States and England the commonest cause of poisoning of the type described here is contamination of the food with living bacteria belonging to the Salmonella group The commonest offenders are *Bacillus enteritidis and B aertrycke* Occasionally *B suipestifer* is at fault and occasionally one finds *B paratyphosus* A or B There are good reasons for believing that these strains of *B paratyphosus* commonly come from rodents in which animals they are present in the carrier state They may be innocuous to the host but they are virulent for other susceptible animals and for man Usually they produce an acute enteritis in man and sometimes they even invade the tissues but they seldom produce a typhoid type of long-continued infection with fever Occasionally

they can be grown from the patient s blood and often they produce easily demonstrable agglutinins

Rats and mice are exceedingly subject to epidemics due to bacteria of the Salmonella type and after recovery a considerable number of the animals are left in the carrier state In one census of rats caught in a large city the feces of 4 per cent were found to contain virulent Salmonella Salmonella or Salmonella like organisms have been found also in 24 per cent of swine hence these animals must be looked upon as a reservoir from which food infection can take place Mice in the carrier state are particularly dangerous in bakeries where their droppings can get into the cream fillings for pies choco late éclairs and cakes Because this filling material is often allowed to remain warm in large batches for hours at a time it can serve as an excellent culture medium for toxin producing bacteria

During recent years more and more out breaks of severe poisoning have been traced to infection of food with staphyl ococci and in some streptococci were at fault In a few cases of acute gastro enteritis dysentery bacilli seemed to be the causative organisms

Because there are many cases of apparent food poisoning of the bacillary type in which careful study of the material eaten fails to show any of the usual bacteria so far incriminated Savage has suggested that there probably are other organisms as yet unknown which can produce the syndrome Doubtle s as time goes on and more out breaks are investigated intensively new or ganisms will be found and identified as pos sible causes of this type of trouble

Savage concluded from his studies that most of the strains of bacteria which cause food poisoning are of animal origin and that only a few outbreaks are due to bac teria obtained from human carriers That such human carriers can however infect food and thereby cause outbreaks of gastro enteritis has been proved in a number of instances

There is considerable evidence to indi cate that the egg of the duck can pick up virulent organisms as it passes through the oviduct and in an occasional case of poison ing the trouble has been traced to such eggs

In perhaps the largest number of cases the offending food is chopped meat or sau sage This is due, first, to the butcher s care-lessness in keeping the scraps which he later grinds for too long a time at room tem perature second, to the many opportunities for infection of these scraps as they are being handled or as they lie exposed in a basket and third to the tendency of the Salmonella group of organisms to grow rapidly in meat

In some cases it has been shown that organisms or toxins from the animal s intes tine invaded the meat during life or after death before the abdominal organs were removed This type of contamination is per haps most likely to happen on farms or ranches where an animal may be slaugh tered because it is sick

In most cases food poisoning appears to be due to the presence of enormous num bers of living bacteria in the material eaten This is perhaps particularly true when the food is not well cooked or when in summer it has lain for hours at room temperature In other cases especially when the food has been cooked and particularly in the case of home-canned food the bacteria may have been killed but the heat resistant toxins may have been left Experiments have shown that not only are bacteria of the Salmonella group highly resistant to cooking but the toxins can withstand boiling for a while Fortunately the staphylotoxin which pro-duces such acute poisoning is not only de stroyed by boiling but is either much weak ened or else destroyed by a temperature of from 60° to 65° C maintained for thirty minutes

Filtrates from cultures of Salmonella or ganisms do not produce symptoms when fed to human volunteers or to animals but filtrates of cultures of certain staphylococci recovered from food which has caused poi soning will kill mice and will sometimes produce severe vomiting and diarrhea in human volunteers

Symptoms—In cases of food poisoning of the type here described symptoms generally appear in from two to six hours after the food is eaten Jordan has stated that if the symptoms come in from one to three hours after eating the physician should suspect that the trouble is due to a preformed toxin

produced by a staphylococcus In Salmonella poisoning the symptoms are likely to follow after a somewhat longer interval

The symptoms are usually those of violent diarrhea perhaps with retching prostration, abdominal cramps and dizziness In an epidemic the severity of the symptoms will vary with different individuals In most cases the acute symptoms will be over within from twelve to twenty four hours, leaving for several days some anorexia weakness mild abdominal discomfort or an inability to digest a large meal The staphylotoxin commonly produces nausea vomiting salivation diarrhea chilliness sweating abdominal pain, painful muscle spasm and shock In the severest cases the discharges from the stomach and bowel are bloody Recovery is usually complete in forty eight hours

Diagnosis —The diagnosis of acute food poisoning is often difficult and uncertain unless it is known that the patient is one of a group that fell ill about the same time a few hours after attending a banquet If this fact is established and the symptoms are typical there will usually be little doubt about the diagnosis In order to establish the exact cause a bacteriologist should be called immediately he should obtain samples of the food eaten as well as samples of vomitus feces and blood and later he may study the agglutinating powers of the patient s blood for the suspected bacteria

As stated before in many cases it is not possible to trace the poisoning to any one particular food or to any one organism It is often hard to guess which food was at fault because so commonly foods heavily infected with virulent organisms look good and have no distinguishing taste

Prognosis —Geiger and others who have studied large numbers of outbreaks of food poisoning of the type here described have found that, when the diagnosis is correct and other more serious conditions can be excluded the death rate varies from 0 4 to 1.5 per cent

Treatment —Some physicians begin by giving castor oil but this added purge hardly seems necessary or advisable when the patient has been emptying his bowel violently for a day or two The main indication is to replace lost fluids and salts If vomiting has been continuous for hours Ringer s solution should be given by vein In the severest cases it would be well when laboratory facilities are available to watch the changes that loss of fluids and particularly of gastric hydrochloric acid are bringing about in the carbon dioxide combining power of the blood and in its chloride content When large amounts of gastric juice are lost a harmful alkalosis can develop

Usually all that is necessary is to withhold food until twenty four hours after the cessation of the acute symptoms Plenty of water should be given and after the bowel is well cleared out the patient may have some opium As McRobert pointed out, opiates should not be given too soon because the last thing one wants to do is lock up toxic material or pathogenic bacteria in the bowel

After the vomiting stops, the physician may give tablespoonful doses of colloidal kaolin or bismuth subgallate or subcarbonate These materials tend to adsorb bacteria and toxins and to stop bacterial development through the solidification of the intestinal contents

One of the most important details in the treatment of acute food poisoning is a slow return to a full diet Experiments on dogs have shown that the irritated bowel absorbs poorly and sometimes if the patient goes back too soon to a full diet he will continue to suffer with indigestion for months After a day on water alone he should begin with beef tea or a little gruel Next day perhaps if the bowel has quieted and the attack seems to be well over he may have beef or lamb with rice and toast Contrary to the common assumption milk is not always suitable food for these patients If after a couple of days the digestive tract seems to be ready to take up its work again a smooth diet may be prescribed and this should be followed until all the soreness has gone out of the bowel and the feces are solid again

In some cases the patient must be warned not to take laxatives in order to start the bowel moving again What he calls constipation is really a pause in colonic function which must be expected seeing that the bowel has been emptied so thoroughly One must expect to wait for two or three days before it is full enough to overflow normally again This is particularly true when

the foods first eaten contain little residue from which feces may be made

WALTER C. ALVAREZ

BOTULISM

Definition.—Botulism is a peculiar type of food poisoning produced by the toxins of *Clostridium botulinum* and *Cl. parabotulinum*. It differs greatly from other forms of "food poisoning" in that its symptoms are not so much those of a gastro-enteritis as of an acute encephalitis with paralysis of the ocular and pharyngeal muscles. Another peculiarity is the late onset of the symptoms. Usually they appear from eighteen to thirty-six hours after the ingestion of the toxic food, and sometimes the interval has been as long as three or four days.

Etiology.—The cause of botulism is a large, slightly motile, gram-positive, spore-bearing and largely anaerobic gas-forming bacillus which can be found easily in the soil and sometimes in the straw which is used as packing around the jars which the housewife uses for putting up vegetables and fruits.

There are at least three types of *Clostridium botulinum*, designated A, B and C. Type A usually produces the most concentrated toxin. This is sometimes so powerful that 1 part in 10,000,000 will injure a mouse. The amount of toxin produced depends on the nature of the food, on the pH, on the amount of sugar present, and on other factors modifying the medium.

In the United States the most dangerous toxin producers among the foods have been, in order of frequency, string beans, corn, spinach, olives, asparagus, beets and apricots.

In Europe most of the trouble has been due to toxin formation in sausages and meat and fish pastes; in the United States most of the outbreaks now follow the eating of home-preserved vegetables or fruits served cold as salad. Years ago commercially canned foods were often at fault, but after intensive research K. F. Meyer and his associates showed the packers how they could always be sure of destroying the highly heat-resistant spores that were causing all the trouble. Since then it has been the home-preserved foods that have caused the outbreaks of botulism.

The great difficulty with home canning comes in sterilizing the containers and the food without the use of steam under pressure. Since some of the spores can survive boiling for six hours or subjection to steam under 15 pounds pressure for six minutes, it is easy to see why they sometimes survive the amount of boiling to which they are submitted. Another difficulty arises when the housewife fails to realize that with some packs it takes a long time for enough heat to penetrate into the center of the jar to bring the contents up to the temperature of boiling water.

Morbid Anatomy.—The most significant finding at necropsy is usually congestion and edema of the central nervous system, perhaps with small thromboses and hemorrhages. The meninges are injected, particularly over the base of the brain. Bronchopneumonia is common. All of the abdominal organs are likely to be engorged with blood and the parenchyma of liver and kidneys will be partially degenerated. According to Dickson and Shevky, botulinus toxin impairs the function of nerve endings, particularly in the parasympathetic system. The poisoned nerves can transmit a few strong stimuli, but they soon become fatigued.

Symptoms.—Usually within from eighteen to thirty-six hours after eating spoiled food the patient begins to feel tired and weak. There may be some dizziness and headache, and the bowels usually become obstinately constipated. In only a third of the cases there may be at the beginning signs of irritation of the digestive tract, as nausea, vomiting, diarrhea and abdominal pain.

Then will come disturbances of vision, diplopia, loss of accommodation, mydriasis and drooping of the upper lids. Later there will be great prostration with difficulty in swallowing and speaking, and finally the patient will be unable to swallow without strangling. The saliva becomes thick and ropy and very hard to get out of
There rarely are any sensory
and the mind is usually clear until

The pulse becomes fast and the
ture falls. Most commonly death
through respiratory failure or from
monia. Most of the patients die
to eight days after eating the
If they succeed in living past the
they are likely to recover. Many who

produced by a staphylococcus In Salmonella poisoning the symptoms are likely to follow after a somewhat longer interval

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OTHER TYPES OF INJURY DUE TO FOOD

So long as certain bacteria and cocci do not enter into the process the putrefaction of meat or fish or casein does not seem to produce any substance which the digestive tract cannot handle with ease Lumholtz the explorer described Australian savages gorging themselves on the meat of a stranded whale which was so high that it could be smelled for miles inland and Stefansson has told of Eskimos eating with impunity fish which had been piled up and allowed to rot for months until it resembled Limburger cheese

Impure milk and ice cream made from it are common sources of gastro enteritis especially in the hot summer months The principal sufferers are infants and children Again the trouble is due to contamination by bacteria derived from an infected udder or from manure dirty cans flies or the unclean hands of human carriers At times cheese becomes toxic when the producer fails to exclude certain bacteria from his vats The outstanding symptom following the eating of such cheese may be a severe headache

Many allergic persons are more or less violently poisoned by certain foods but this topic will not be taken up here because in these cases it is not the food but the consumer who is at fault

There are a number of edible plants which are somewhat poisonous and some like manioc and *sweet potatoes* which are poisonous in the raw state can be prepared in such a way as to be harmless *Sprouting potatoes* eaten raw are particularly dangerous The symptoms are vomiting diarrhea colicky pains headache prostration constriction in the throat stiffness of the tongue marked mydriasis or miosis disturbances in vision and hallucinations Certain types of vetches such as *Lathyrus sativa* and the *Cicer* or chick pea can produce poisoning in countries in which large amounts of this food are eaten The main symptom is stiffness in the legs

In some parts of the world such as Japan and Hawaii certain fishes must not be eaten because they are poisonous and at certain unpredictable times of the year mussels are exceedingly so Recently it has been learned that this is due to the presence of myriads of little dinoflagellates The first symptom of poisoning which comes soon after the food is eaten is a feeling of numbness and prickling about the mouth This should be the signal for a prompt emptying of the stomach

Ergotism is due to the long continued eating of rye which has been infected with the fungus *Claviceps purpurea* The symptoms are those of injury to blood vessels

As is well known the eating of certain types of mushrooms, particularly the *Amanita phalloides A muscaria* and *A verna* leads to severe poisoning not only by muscarine but by several other toxic substances. Perhaps because the toxins are different there are two main types of mushroom poisoning In one—the more hopeful so far as treatment is concerned—the symptoms are largely those of gastro enteritis with diarrhea vomiting abdominal colic great thirst and collapse In the second and more fatal type the symptoms are largely those of injury to the nervous system with headache, somnolence trismus mydriasis sometimes opisthotonos with other forms of muscular crampings perhaps blindness loud cries and finally coma

The symptoms commonly appear in from four to five hours after the meal Atropine is the antidote for muscarine and should be given in large doses The stomach should be emptied and when there is much destruction of the blood transfusions should be given Solutions of dextrose may be administered intravenously to help protect the badly injured liver According to Limousin and Petit (1932) the fresh chopped brains and stomachs of several rabbits given by mouth will combine with the toxin and act as a specific

Fruits, and particularly apples when heavily indulged in can be dangerous if they have been sprayed with salts of lead and arsenic used to eradicate insect pests For some time the United States Government has been taking measures to obviate this danger Many persons fear that they will be poisoned if they eat food cooked in aluminum pots but there is no foundation for this phobia Aluminum hydroxide is now given in large doses to patients with peptic ulcer and they are not poisoned

WALTER C ALVAREZ

survive the intoxication succumb to an inhalation pneumonia which arises from their inability to swallow properly During the illness the digestive tract often seems to be paralyzed and food remains for a long time in the stomach

Diagnosis —This may be easy when a number of persons who ate at the same table fall ill about the same time with the typical ocular palsies or when the patient remembers having eaten food which looked spoiled and tasted peculiarly or when on a farm chickens given spoiled food are dying with ' limberneck When only one person is ill the problem of diagnosis is more difficult and the physician may think of encephalitis or poliomyelitis or of the various other causes of bulbar paralysis or ophthalmoplegia If any of the suspected food can be secured an expert can soon tell whether or not it contains the toxin of *Clostridium botulinum* If it does a small portion injected into a mouse will soon cause paralysis and death

Prognosis —The prognosis is bad In the United States two thirds of the victims die In Germany the disease is often milder and the mortality lower

Prevention —The prevention of botulism depends largely on the success of campaigns to educate housewives not to take chances with food from home packed jars especially when spoilage has taken place as shown by leakage over the rubber ring

At times, the infected food will look spoiled it may be softer than it should be it may contain gas bubbles or it may have a cheesy or rancid smell On the other hand infected food may look all right and it may fail to give off a peculiar odor even when it is warmed

In some cases the toxin has been so concentrated that simple tasting of the food by the cook has led to her serious illness Home preserved food which has bubbled over or has shown any other signs of spoilage should not even be tasted Nor should it be thrown out in the barnyard because this leads commonly to the death of chickens and other domestic animals

As one cannot always detect signs of spoilage the only safety lies in boiling all home-preserved foods for at least six minutes before they are served to destroy any toxin that may be present Because this amount of boiling will not destroy spores and because it is still a question whether or not they can grow in the body and there produce dangerous amounts of toxin it is not *advisable to boil and eat definitely spoiled food* The worst thing the housewife can do is to cover up the taste of slightly spoiled food with some form of dressing and then serve it unheated as a salad To do this is to invite disaster which may wipe out the whole family

Treatment —The best treatment of course is prevention Once the typical symptoms have appeared the patient is likely to go downhill in spite of any therapy If the antiserum can be obtained quickly it should be used because evidence is accumulating that it sometimes saves life Naturally there is much more chance of its doing good when it is given before paralysis appears Unless the type of the infecting organism is known a polyvalent serum will have to be used After first testing the patient for sensitiveness to horse serum one large dose of from 5000 to 10 000 units should be given intravenously

Every effort should be made to protect the patient from fatigue and a little morphine may have to be used to lessen suffering If the patient is seen early, it may help to wash out his stomach since this organ tends to retain the offending food for several days Care must be taken however lest the procedure induce dangerous fatigue and strangling Any feeding that is attempted should perhaps be done with the help of a fine Levin tube through the nose Food given by mouth is likely to produce strangling and pneumonia Perhaps the sticky ropy mucus that is so troublesome can be wiped or sucked out of the throat Small doses of ipecac or emetin will sometimes loosen it and thus bring great relief

It is possible that more patients would be saved from a respiratory death if they were placed in a respirator The danger from pneumonia can be lessened by the use of the oxygen tent or B L-B mask as soon as the first signs of cyanosis appear Because the muscles can so easily become paralyzed with effort every precaution should be taken to spare the patient exertion

WALTER C ALVAREZ

saved the site of the bite shows a ragged and indented scar from destruction of tissue

On the other hand after the bite of the cobra there is slow and moderate swelling and little or no discoloration The first major symptom is difficulty in breathing and this is steadily progressive If recovery takes place it is rapid with but little destruction of tissue at the wound

Between these extremes are various ratios of the toxic elements producing a variety of symptoms Some of the African vipers produce a combination of tissue destruction and neurotoxic reaction The North American rattlesnakes the copperhead and the moccasin produce largely hemolytic reaction but their predominating hematoxin is not of such sinister or rapid effect as that of the Central and South American vipers Then again the relative toxicity varies among them Drop for drop the venom of the copperhead is not so powerful as that of the rattlesnake and while the poison of the water moccasin is slower in effect than that of a rattlesnake and more quickly neutralized with *antitoxin its necrotizing effect if* unrestrained is ultimately more pronounced The small and gaudily colored coral snake of our southern states with a number of allies in the tropics is a degenerate New World ally of the cobra It secretes a powerful neurotoxin

For the injection of venom the serpent is provided with a pair of highly specialized teeth in the anterior portion of the upper jaw With the viperine types these teeth are quite the duplicate of the hypodermic needle having an orifice at the tip whence the poison is discharged Each fang or hollow tooth connects with a venom gland situated in the temporal region of the head With the viper the fangs are of such excessive length that they are necessarily folded back against the roof of the mouth when the jaws are closed They are attached to movable bones With the cobras and their allies the fangs are short but stout and permanently erect

Against this race of formidable creatures man has been studying and battling for years for a remedy The high human mortality in India amounting to more than 20 000 lives a year inspired Albert Calmette of the Pasteur Institute to experiment with antivenom sera more than thirty years ago A noted expert on the poisons of reptiles and insects he recognized the varying types of poisons in different snakes His early experiments were with a polyvalent serum produced by immunization of horses with repeated and stepped up injections of a mixture of cobra and viper venoms Later on, he found that specific immunization with the poison of one particular type of snake was far more efficacious This is now the general practice in the production of all antivenom sera The usual time necessary to produce immunity in a horse is now six to eight months After this period the animal develops remarkable resistance readily enduring many times the lethal dose of venom The neutralizing effect of such sera has been greatly strengthened during the past ten years by filtration processes which produce high concentration

A fine institute for the study of snake venoms has been developed at Sao Paulo Brazil under the auspices of that government As an example of the economic value *of this work it should be noted that thirty* years ago Brazil recorded several thousand deaths a year from the bites of snakes Careful tabulation recorded less than 50 deaths during 1929 Several types of serum are widely distributed One is for the bushmaster or surucucu another for the fer-de-lance (jararaca) and allied species another for the rattlesnake and a distinct serum for the coral snakes

A careful tabulation carried over several years indicates an annual mortality of about 100 lives in the United States Several hundred cases of snake bite occur each year but in many instances recovery takes place The Antivenin Institute of America at Glenolden Pennsylvania has a scientific consulting board and a series of subsidiary stations in various parts of the country each in charge of an accredited expert This institute produces a polyvalent serum for the bites of the rattlesnake moccasin and copperhead The venoms of these three types largely of a hematoxic nature are similar enough to render a single grade of serum entirely practical and efficacious

Treatment —The writer has been surprised to note the general lack of understanding of the treatment of snake bite in

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SNAKE VENOM POISONING

The actual composition of snake venom is not altogether clear One of the best definitions is that of Dr Adolph Monaelesser which may be briefly stated as follows Snake venom is composed of a mixture in variable proportions of protein substance mucus and debris of epithelial cells some fatty matter, and salts such as calcium chloride and phosphate also ammonia and magnesia The density is somewhat greater than that of water, varying in specific gravity from 1 030 to 1 050 The proteins contain the various active toxins which by certain methods can be removed or some of them inactivated as has been demonstrated by researches in the New York Zoological Park'

The fresh venom of different snakes varies in color from deep amber to yellowish green straw color or almost colorless and is in gross appearance a viscid fluid The dried venom is quickly soluble in distilled water It retains its full toxicity for years if kept in darkness but slowly deteriorates if exposed to light Owing to its contamination with bacteria from the reptile s mouth it quickly decomposes if left in a fluid state

Grossly speaking the venoms of all serpents are composed of two primary elements a hematoxin and a neurotoxin The former creates great destruction of the red blood cells and tissue It causes extensive swelling discoloration by extravasation and certain other manifestations The other primary element neurotoxin produces little swelling but its action is quite as formidable as the action of hematoxin It attacks the nerve centers particularly the sympathetic system, also the phrenic nerve The thoracic muscles become paralyzed to such an extent that the victim may succumb through inability to breathe

The major differences in snake venoms are due to varying proportions in the hematoxic or neurotoxic elements These elements also differ in their relative toxicity among various species of serpents Analyses indicate that each of the elements is complex in composition and that these components when separated may produce certain local manifestations distinctly recognizable from the broader symptoms of the combined element

As examples of the varying proportion of the hematoxic and neurotoxic elements we may take the prevailing viper of the American tropics and the Indian cobra They represent the two extremes The viper is known under various names In Central America it is called the *barba amarilla* and in Martinique and St Lucia the only islands in the West Indies where it occurs it is commonly termed the *fer de lance* In northern South America it is usually referred to as the *mapepire balsayn* and in southern Brazil as the *jararaca* The symptoms following its bite are rapid and extremely dramatic Immediate swelling and discoloration take place There is an oozing of blood from the mouth the conjunctiva and even from the stomach during the reflex vomiting which frequently occurs with the greater number of snake bites There are bloodlike ejections from the bladder The victim sinks into a condition of coma and death may result in six to twelve hours These symptoms point to a poison with extremely potent hemolytic action The blood stream is so thinned and the walls of the vessels so broken down that there is a tremendous leakage over great areas If the injection of a neutralizing serum is delayed in such cases a blood transfusion is usually necessary to save the patient If the patient is

DEFICIENCY DISEASES

INTRODUCTION

The nutritional deficiencies are a group of diseases caused by an inadequate intake or absorption of essential food factors The inadequacy may be on the basis of usual or normal requirements or may be a relative inadequacy a failure to meet abnormally increased needs Though often thought of as referring only to vitamins the essential food factors include the energy principle (calories) protein and certain amino acids some minerals and perhaps fatty acids as well In medical practice deficiencies of single factors alone are rarely encountered nearly always they are multiple although usually the signs and symptoms of one or two predominate Curiously complete starvation is not accompanied by evidence of deficiencies other than calories

Although the effects of many of the deficiencies are represented by well known syndromes such as pellagra and scurvy and the symptoms of a deficiency of such factors as salt have long been clearly recognized as deficiency states the modern concept of deficiency disease really begins with the discovery of the vitamins These substances were hinted at by Lind s classical observations on lime juices and scurvy but had their real beginning in the search for the substance in rice bran that cured polyneuritis in pigeons an unknown substance to which Funk gave the name vitamine From these studies came the impetus for the discovery of not only thiamine (Vitamin B_1) but nearly a dozen other vitamins and a new concept which has brought together old and new syndromes in a group of diseases with well-defined characteristics Furthermore study of these substances their functions and the effects of a deficiency in them has greatly increased our knowledge of physiology as well as our clinical knowledge of disease

In the beginning medical interest and knowledge were confined to the gross manifestations of severe deficiencies These disclosed themselves as well known classical diseases whose etiology and pathogenesis had long been obscure—scurvy beriberi pellagra hunger edema keratomalacia and others As further progress was made new essential nutritive elements and the syndromes due to their deficiency were discovered—vitamin K and the hemorrhagic states related to it for example New and hitherto unrecognized results of the deficiencies of previously known factors were found Finally it has become known that besides the severe and advanced deficiencies hitherto recognized there are many instances of deficiencies so slight that either they cause no recognizable symptoms or they produce symptoms too mild and nonspecific to constitute reliable diagnostic evidence of the deficiency To detect such deficiencies objective laboratory tests and special procedures are required and as the need for these arises they are rapidly being developed

The various nutritive factors and the diseases associated with them have many characteristics which serve to distinguish them as a group Except for the energy principle and protein the various substances are needed in very small amounts much as catalysts or enzymes This is true even of certain minerals the nutritive requirements of which are many times smaller than the pharmacologic doses Even for protein the required amounts of the *essential* amino acids are relatively very small

None of the essential factors can be formed or synthesized by the body they must be obtained in a preformed state in the diet This characteristic which is relative and shows considerable species variation is well expressed in man He can complete the synthesis of vitamin A from carotene can obtain vitamin K from the action of bacteria in his intestine and can form vitamin D from the action of ultraviolet light on his integument Except for these limited abilities he is dependent on preformed substances from outside sources

Another characteristic of the various nutritive factors is their relative lack of toxic-

various parts of this country Unfortunately, cauterization is frequently employed, but a lethal fluid has been hypodermically injected and the first thought should be to prevent its absorption by ligation this to be immediately followed by drainage Ligation and incision should be the first steps after snake bite

We are constantly learning more about the action of snake poison Dudley Jackson of San Antonio Texas has recently demonstrated that a considerable portion of the injected venom lingers in the bitten area for some time This indicates the necessity for *incision* to invade the fang punctures and the desirability of immediate *forced suction* from the area of the wounds Suction devices similar to breast pumps have been found highly efficient and serous accumulation thus removed several hours after from the area of a severe bite has been found to contain heavy traces of venom There is a rapid and notable accumulation of serum in the bitten area This is usually discharged in profuse quantities from the drainage incisions which should be covered with dressings kept wet with some mild antiseptic

Antivenom serum is most efficacious when injected immediately after a bite but it should be administered even if the victim has already approached a condition of collapse *In delayed cases however the serum* is usually injected too late to be properly taken up by the circulation and thus neutralize the venom injected at the time of the bite

The bite of a copperhead or small rattle snake is not ordinarily fatal although it may be very serious Serum may be injected as late as a day or even two days after the symptoms of swelling have developed It is far better however, to inject it as soon as possible in order to quickly neutralize the poison and thus prevent destruction of the blood corpuscles A large rattlesnake may inject enough poison to produce death in ten to twelve hours or in a much shorter time if as occasionally happens a vein is punctured Ordinarily serum is injected subcutaneously in the abdominal region or between the shoulder blades If extremely rapid and alarming symptoms develop the safest course is to administer the serum intravenously

The blood stream has the property of neutralizing a certain amount of poison Consequently, in a large-bodied adult with full blood content, not so much serum may be necessary as with a small and slight person *Thus it should be understood that considerably more of the neutralizing antivenin* is necessary with a child and while 20 cc of serum may be found all that is necessary to produce a rapid alleviation of symptoms with a large adult, at least 30 cc or more may be necessary with a very young person The first injection should be 10 cc to be repeated at intervals, until there is a definite and favorable reaction

Both ligation of the wounded area with frequent slacking and repeated suction should be employed It may be necessary to continue this treatment for several hours after the bite and if the swelling is extremely extensive small cruciform incisions over the swollen area are indicated Such incisions kept moist will allow profuse serous drainage

The local use of *permanganate of potassium* except in very mild solution will result in destruction of tissue Used in extremely dilute solution (1 2000) in the immediate wound areas permanganate may *oxidize a certain amount of the venom* but it does little good owing to its lack of penetration However it has germicidal properties It is utterly rash to rub pure crystals of permanganate into the wounds Nothing could be more foreign to the treatment of snake bite than such practice

As not only the immediate area of the wound but a considerable portion of the neighboring tissue is much damaged and therefore, subject to secondary *bacterial invasion* and as the bite itself sometimes is attended by specific infection from microorganisms in the snake s mouth, the wounds should be kept covered with a wet and mildly antiseptic dressing for several days or until a time when all symptoms of swelling are gone Such wounds are usually stubborn and may remain open for several weeks

RAYMOND L DITMARS

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INTRODUCTION

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ity or potentiality for harm Excessive amounts are in general excreted without untoward effect, even of such minerals as iodine, if the amounts are at all near the range of nutritional requirements This lack of untoward effect, however is concerned with a direct toxic action and not with possible ill effects of a nutritional nature caused by an imbalance of nutritive factors Little is known of possible disturbances of this kind, but there is sufficient evidence to indicate that such disturbances can occur A simple example is the increased requirement for thiamine caused by an increased carbohydrate (calory) intake

All of the known essential nutritive products are distinct chemical substances The nature chemical composition and structure of *most of them are known Many of the* organic substances have been isolated and synthesized—one of the most brilliant achievements of modern chemistry In a number of instances the specific factors are members of a related group of chemical substances natural and artificial some of which may possess an effect similar to that of the specific nutritive factor Usually such related substances have a less marked effect than that of the specific factor occasionally (vitamin K) the action of a related even an artificial compound is greater than that of the natural essential substance

Because these nutritive essentials are known chemical substances we have considerable knowledge of their physical characteristics and reactions Much is known of even the biochemical behavior of many of them For example many members of the so called B complex of vitamins are concerned in oxidation reduction reactions involving the transfer of oxygen and hydrogen in the intimate biologic processes of metabolism Thiamine is known to play an important and necessary role in the end stages of the oxidation of glucose Yet the relation of such functions and reactions to disturbed physiology the mechanism by which even known alterations in physiology produce clinical signs and symptoms characteristic of the specific deficiencies remain unknown in most cases Recently more subtle functions and reactions such as those concerned with detoxification mechanisms immune body production and the like disclose new fields of study and development and suggest nutritional disease of a kind not manifested in the usual recognized manner but as a disturbance in metabolic processes concerned with exogenous and endogenous toxins and in the response to other disease. It is apparent that such actual nutritional deficiencies as occur under these circumstances will be of the so called conditioned type

As a group the nutritional deficiencies that is the diseases resulting from a lack of the specific nutrients have many characteristics in common as do the nutritive factors themselves Clinically these deficiency diseases appear in epidemic as well as in endemic and sporadic form The sporadic cases are of more immediate interest to *practicing physicians but existing endemic* deficiencies provide a large backlog of nutritional disease which constitutes a threat of complication in all manner of other disease and under conditions of stress often develops into a major problem by *itself*

Clinically a distinction is also made between those uncomplicated deficiencies which develop independently as the result of a failure of the nutritive supply and those which are brought about by the influence of some other disease on the intake or absorption or utilization of food The latter are known as conditioned deficiencies They constitute the largest group of deficiencies seen in medical practice and because of the fundamental nature of nutrition are found in all specialties and types of practice More and more the conviction is growing that most of the recognizable deficiencies even of the milder grades are the result of some individual circumstance or condition which precipitated or conditioned a deficiency More and more it is being recognized that many of these relationships are of a subtle kind concerned with infection with metabolic disorders with chemotherapy and hence less nutritional than metabolic In this direction lies much of the future development in the field of nutrition In many instances however the development of these conditioned deficiencies is made possible by the existence of a mild endemic type of primary nutritional deficiency common to many of the population

So far the goal of clinical medicine *in the*

prevention and control of nutritional de ficiencies has been the absence of disease , little has been done in the direction of positive health Little is known of optimum nutrition or even of optimum amounts of single factors The problem is exceedingly complex concerned as it is with the inter action of a large number of independent major nutritive factors besides many lesser influences Yet in the direction of such optimum nutrition lies a potentially tremen dous advance in public and individual health

JOHN B YOUMANS

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SCURVY

Definition—Scurvy is a nutritional dis order caused by prolonged inadequacy of the diet in vitamin C (ascorbic acid) In its mild forms it gives rise to apathy anorexia fatigability and loss of strength with ten derness of the extremities or even of the whole body, to these symptoms is added in more severe cases a striking tendency to hemorrhage The manifestations of the dis ease depend to some extent on the age of the patient Infantile scurvy (Barlow s dis ease or Moeller Barlow disease) differs from adult scurvy principally in the extent to which the growing bones are involved but discrepancies in morphology and symptoma tology based on the patient s age level do not justify separation of the resulting syn dromes into two entities for they are of one etiology

History—The name scurvy appeared first in the Middle Ages as a folk word having various forms phonetically allied in several European tongues Its ori gin is therefore obscure The Latinized "scorbutus" is an artifi ial implant

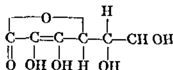
Whether scurvy was observed by Hippocrates is a matter of dispute Possibly the earliest clear-cut descrip tion of the di ease was made by de Joinville whose ac count of its appearance among the Crusaders of the thirteenth century leaves no room for doubting its iden tity Its ravages in mar time voyages during the Age of Discovery were appalling Scurvy cost Vasco da Gama 100 lives among his crew of 160 men in his voyage around the Cape of Good Hope in 1497 and disabled all but 10 of Jacques Cartier s crew of 110 men on their expedition to Newfoundland in 1 35 To Joseph Lind an officer of the British navy belongs the credit of amassing convincing evidence first, that scurvy is a disorder of nutrition and not a contagion or strictly an occupational disease and second that it results not from excessive consumption of certain articles of diet but from insufficient intake of others His 'Treatise on the Scurvy" published in 1753 was ultimately respon sible for the introduction of lemon juice into the sea man s ration Sharp as was the decline in the general morbidity of scurvy after the widespread adoption of effective preventive measures the disease has neverthe less continued to appear in circumstances of stress For years the incidence of scurvy in Ireland bore a recipro cal relation to the success of the potato crop In the siege of Paris in 1870 and 1871 the disease ravaged both the military and the civil population it appeared among the troops of both contestants on various fronts of the World War of 1914–1918 especially in Russia, Rumania and Mesopotamia, and among the people of Austria during the postwar economic depression

Infantile scurvy has a somewhat different story Glisson whose treatise on rickets was published in 1650 had seen scurvy in London children and had ascribed it to defective environment In 1859 and again in 1862 Moeller of Konigsberg reported cases of what he called "acute rickets the descriptions of which are clearly those of scurvy· this erroneous interpretation of nosologic evidence spread a cloud of confusion over virtually the entire Germanic school of medical thought. Barlow of London in 1883 published indubitable ana tomic evidence that scurvy may affect infants His view was accepted as authoritative throughout a large por tion of the Western World although most Germans continued for decades to regard the identity of "die Moeller Barlowsche Krankheit" and infantile scurvy as open to question Modern chemical studies have dis pelled all doubt.

Scurvy was produced in laboratory animals by Theobald Smith in 1895 but the discovery was not followed up The experimental period began actually with the work of Holst and Frolich which was pub lished in 1907

In 19 8 Szent Gyorgyi isolated from the suprarenal glands of oxen and from various plant sources a crystal line compound of formula $C_6H_8O_6$ which he named hexuronic acid The wide distribution of this com pound in animal tissues and in growing plants was soon appreciated as were also its strong reducing properties but it was not until 1932 that Szent-Gyorgyi determined by appropriate feeding experiments that he had been dealing with the specific antiscorbutic factor vitamin C Simultaneously and independently King and Waugh isolated a highly active antiscorbutic compound from lemon juice and showed that it was identical with "hex uronic acid By common agreement the latter term was abandoned in favor of ascorbic acid by which the pure vitamin is now universally designated The American Medical As ociation for a time advocated the name cevitamic acid

Etiology Chemistry of the Vitamin.—The structural formula of the vitamin is



This is the *l* form the *d* form has no anti scorbutic activity It is readily soluble in water methyl alcohol, ethyl alcohol and acetone, and is precipitated by lead In watery solution in the presence of traces of heavy metals (*e g* copper) acting as catalysts it takes up atmospheric oxygen rapidly with resulting loss of antiscorbutic activity The rate of oxidation is accelerated by heat light and by alkalinity of the medium The assay of biologic fluids for ascorbic acid content depends on quantitative reduction of reagents under specific control of the medium in which the reaction takes place Methods now in common use employ either 2 6 dichlorophenol indophenol or methylene blue as both oxidizing agent and redox indicator

The part played by vitamin C in physico chemical mechanisms *in vivo* is still obscure It is thought to be involved in physiologic oxidations in addition it is known to be essential for the proper formation of collagen by fibroblasts, and there is indirect evidence that it participates in the production of intercellular material in other tissues but the details of these reactions have not been elucidated In premature infants the administration of ascorbic acid suppresses the urinary excretion of hydroxyphenyl lactic and hydroxyphenyl pyruvic acids

The juice of ripe oranges has a fairly constant content of vitamin C at about 0 5 mg per cubic centimeter Other citrous fruits though showing greater variation under market conditions contain similar quantities In general there is a fairly close parallelism between the ascorbic acid content of plant tissues and their store of carotenoids or chlorophyl, green leaves and shoots of all kinds as well as tubers whether edible or those generally regarded as inedible are sources of vitamin C

In animal tissues the concentration of ascorbic acid is highest in the adrenal hypophysis corpus luteum lens and aqueous humor and somewhat less high in brain pancreas liver spleen and kidney it is considerably lower in muscle tissue distinctly low (about 0.5–1 5 mg per cent) in blood plasma and virtually absent from fat Human milk normally contains from 4 to 7 mg per cent of ascorbic acid, depending partly on individual performance partly on fluctuations in the vitamin C content of the mother s diet Cow's milk while it has only one third or one quarter as much vitamin maintains a constant level at all seasons since the concentration is independent of the vitamin C content of the fodder Chemical synthesis of ascorbic acid now competes successfully with its isolation from natural sources

The human organism is unable to synthesize ascorbic acid and it is this dependence on intake which determines susceptibility to scurvy From a number of sources evidence has been adduced to indicate that the daily metabolic requirement in man—the quantity of ascorbic acid normally utilized in the body—is about 1 mg per kilogram of body weight When the dietary supply exceeds this amount, retention occurs until the stores are filled after which loss through urinary excretion takes place above a threshold level of approximately 1 5 mg per 100 cc of plasma On an average diet the normal adult excretes from 5 to 50 mg of ascorbic acid in the urine in twenty four hours An increase in the intake augments this output though not immediately and not quantitatively If to an average diet one adds a daily supplement of 500 mg of ascorbic acid equivalent to about 1 liter of orange juice the urinary excretion of the vitamin will rise significantly within the first or second twenty four hour period and will level off at about 80 per cent of the intake After this equilibrium has been established withdrawal of the supplement results in a similarly steep falling off of the excretion, so that within three or four days the output has returned to the starting level It would seem in other words, that the organism has a limited capacity for storing vitamin C that on an average diet the stores are not filled to the saturation point, and that after saturation the major portion of the intake spills over into the urine The fate of the unaccounted fraction of the supplement is unknown at the present time evidently it is not destroyed in the alimentary tract nor excreted in the stools for intravenous injection of the supplement gives virtually identical results the supplement appearing in the urine more promptly but only slightly more completely Infections and hyperthyroidism accelerate vitamin depletion Withdrawal of vitamin C from the

diet of a normal subject for a period of one or two weeks causes a clearly detectable change in the economy of the vitamin when a supplement is subsequently added the daily administration of a liberal quantity of ascorbic acid following such a vitamin free period may fail to produce an increased output in the urine for four days or even longer

In cases of manifest scurvy the body stores of ascorbic acid are significantly depleted the plasma concentration is zero or nearly so and the small quantities reported present in urine may well reflect merely the error of analysis In the depletion process the white blood cells and platelets which normally contain ascorbic acid at a concentration some thirty times as great as that of cell free plasma retain their stores with relative avidity yet they likewise lose their titrable ascorbic acid by the time scorbutic symptoms appear On therapeutic administration of the vitamin relief of symptoms and signs of scurvy precedes the restoration of a normal urinary output of ascorbic acid or the establishment of a stable plasma concentration at a normal level

The time required to bring out symptoms of scurvy on a deficient diet varies greatly in ordinary clinical circumstances partly because complete deprivation is seldom encountered except under experimental conditions partly too because of the delaying effect of even a small intake of the vitamin In a notable human experiment carried out by Crandon under controlled conditions of strict dietary deficiency the subject s plasma level of ascorbic acid fell to zero by the forty first day the white blood cells and platelets became depleted after four months yet objective signs of scurvy in the form of cutaneous hemorrhages were not evident until the 161st day of the experimental diet These intervals presumably represent approximately minimal values Subjective symptoms of a less specific nature—languor fatigability and anorexia—evidently preceded the appearance of objective signs of scurvy but their import became clear only in retrospect when the resumption of an ample vitamin intake promptly dispelled them Most cases of scurvy seen in infancy develop six months or so after the institution of artificial feeding A few examples have been reported in infants considerably younger but in these instances the mother could invariably be shown to have subsisted on an inadequate diet during pregnancy, and the period of vitamin C deprivation so far as the infant was concerned obviously commenced before birth Many examples are on record of scurvy breaking out in a ship s crew within a few weeks of sailing but here one is inclined to incriminate the on shore diet and to suspect that the subject was in a state of relative deficiency at the time of embarkation It is quite evident that between the state of replete stores and that of active scurvy there is a broad zone in which a subject may be symptom free and yet subsist on a demonstrably low turnover of ascorbic acid

Pathology—In fatal cases of scurvy in adults hemorrhages into the skin are found as a rule in only one of the twenty three cases reported by Aschoff and Koch were superficial hemorrhages absent They may vary from the smallest petechiae to large ecchymoses The larger spots are apt to be found on the trunk the smaller ones on the extremities Almost invariably the lower extremities are more markedly involved than the upper the face palms soles lateral aspects of the thigh and region of the knee joint tend to be spared Many of the hemorrhages involve hair follicles or at least begin there keratosis pilaris frequently occurs in association with the disease

Edema and accumulation of fluid in body cavities are characteristic of scurvy the transudates remaining strikingly uncontaminated with blood Localized areas of superficial edema are apt to overlie deep hemorrhages which occur most frequently in the lower extremities both because of their increased liability to trauma and because of the greater hydrostatic pressure to which their blood vessels are normally subjected Such hemorrhages appear to arise from capillary oozing rather than from macroscopic rupture of a larger vessel but they may attain almost any size Intramuscular hemorrhages are common at sites of particular mechanical stress Subperiosteal hemorrhages are relatively uncommon in adult scurvy but invariably accompany severe cases of infantile scurvy owing to loosening of the periosteal attachment which is a primary feature of

the functional pathology of the disease capillary bleeding *may dissect the periosteum* free over a large area Most commonly these subperiosteal hemorrhages are found at the lower end of the femur, the upper end of the humerus both ends of the tibia and at the costochondral junction of the middle ribs but they may be found in almost any location in severe cases as over the skull the clavicles, or the *scapulae*

The lesions of the gums will be described among the clinical signs Scurvy causes striking changes in the teeth separation of the odontoblast layer from the dentin and development of hemorrhages within the pulp cavity Although the teeth are capable of functional recovery the healing process is never anatomically complete so that histologic identification of an antecedent attack is possible throughout life

In growing tubular bones particularly in those having normally a rapid rate of growth, such as the middle ribs the histologic changes occurring at the cartilage shaft junction are characteristic the lattice of calcifying cartilaginous matrix is the site of numerous microscopic fractures the formation of trabecular bone by osteoblasts is in abeyance and the intervening marrow spaces at the end of the shaft are filled with a loose connective tissue framework con*taining hemorrhages and collections of fibrin* So greatly is the strength of the bone compromised by these processes that it offers relatively ineffectual resistance to the stresses accompanying normal activity, and the epiphyseal cartilage may be comminuted into the shaft or sheared off to one side carrying with it the periosteal attachment and a thin disk of calcified lattice

Symptoms —The symptoms of the disease begin as a rule insidiously with a feeling of general weakness and inadequacy negativism depression or even melancholia The normal degree of alertness is replaced by a disposition *to inactivity the patient* preferring to sit down or lie about The appetite fails and the taking of food is additionally hampered by painful *gums which* are disposed to bleed easily The skin is dry and rough at times dirty looking in more advanced stages so dark as to resemble the color found in hemochromatosis and it may *take on* a waxy appearance from retention of fluid In areas in which capillary pressure *is high as in the lower* extremities or in regions distal to constricting bands of clothing minute hemorrhages are to be seen in the hair follicles (piquete scorbutique)

Increasing mental depression accompanies progressive loss of muscle power The lips become cyanotic and the gums begin to show erosion of the mucous membrane at their *margins with formation of friable black* masses adherent to the teeth almost invariably these are accompanied by fetid breath The lower extremities develop swellings in the muscle masses particularly in the extensors and adductors of the thighs and in the calves and the knees are held in partial flexion, efforts toward full extension are accompanied by great pain There is increased swelling of the subcutaneous tissue of the feet particularly between the Achilles *tendon and the tibia Tenderness on deep* pressure may be elicited in any part of the limb Finally as a most important sign ecchymoses appear especially over the lower third of the thigh above the malleoli or on the dorsa of the feet Hemorrhage into the muscle masses or beneath the periosteum is generally accompanied by induration There may be either microscopic or gross hematuria

Not all of the symptoms mentioned are *necessarily of simultaneous* occurrence The mental depression which is of course relative and nonspecific is rarely absent but ecchymoses may occur in the absence of stomatitis and the disease may be clinically recognizable before extensive intramuscular or subperiosteal hemorrhages have *taken* place

With healing recovery occurs in more or less the following order stomatitis mental depression induration cutaneous hemorrhages and last discoloration of the skin

In particularly severe cases where healing does not take place the course is progres*sively downhill* The necrotic changes in the gums involve the alveolar process the teeth loosen and fall out often with uncontrollable *hemorrhage There may* be hemorrhage from the nose stomach or intestine or an extravasation of blood may suddenly appear without provocation *at some bizarre site* as in the orbit causing proptosis and ecchymosis of the eyelids Suppuration may develop in

any hematoma leading to the formation of huge abscesses The pulse becomes rapid and weak and the patient may suddenly die from relatively mild physical exertion or may expire from progressive prostration

In infants apathy and irritability alternate but anorexia is the rule In contrast to the afebrile state of older individuals elevation of temperature is almost always present Petechial hemorrhages are generally less conspicuous than in the adult The tenderness of the involved extremities and the changes in contour brought about by subperiosteal hemorrhages and epiphyseal infraction are often extreme On the other hand the oral signs are usually limited to swelling and purple discoloration of the gums around deciduous teeth which have already erupted or are about to erupt while the formation of large vegetations is rare and fetor exceptional

Anemia of some degree is the rule in scorbutic infants its intensity depending partly on the amount of blood lost and partly on the severity and duration of the disease process generally for deprivation of the vitamin retards new blood formation The leukocyte pattern is not affected in uncomplicated cases

Scurvy interferes with the healing of wounds and lowers the patient s resistance to superimposed infections of all sorts Of the latter the common complications are pyoderma wound infection oral sepsis pneumonia tuberculosis and especially in infants bacillary dysentery and diphtheria Scurvy often goes hand in hand with other deficiency diseases

Diagnosis —The diagnosis of scurvy is generally made on the history of an inadequate diet combined with the detection of some of the more obvious physical manifestations of the disease Subperiosteal hemorrhage supervening on mild or insignificant trauma is always highly suggestive other sites of bleeding are less specific in their import but any bleeding which does not depend on some demonstrable cause such as thrombocytopenia hemophilia or other defect of the blood clotting mechanism must give rise to a suspicion of scurvy Tenderness may be confined to the region of the long bones of the lower extremities or may at times be so capricious in its orientation as to bring the patient under suspicion of neurosis or even malingering The changes in the gums produced by scurvy may be simulated in thrombocytopenic purpura leukemia or mercurial poisoning

For the verification of the diagnosis roentgen examination of the long bones may be of immediate service provided the patient is young enough for growth of the bones to be still in progress The bone changes of infantile scurvy are pathognomonic and readily recognizable by one who has had experience in this field but in children and especially in young adults they are much milder are liable to be limited to the middle ribs where clearly defined photographs are technically difficult to obtain and only too often are subject to equivocal interpretation Subperiosteal hemorrhage is not ordinarily recognizable in roentgenograms until some days after the institution of effective therapy and until ossification has been resumed in the elevated periosteum

The importance of the demonstration of capillary fragility as an aid in the diagnosis of scurvy has in the past been somewhat overstressed An increase of capillary fragility accompanies most cases of scurvy arising as a result of gross errors of diet often preceding the appearance of other signs of scurvy Gothlin Dalldorf and others have demonstrated that subjects subsisting for long periods on a diet relatively low in vitamin C but still rich enough to obviate the development of frank symptoms and signs of scurvy show petechial hemorrhages when the difference of pressure within and without the vessel wall is insufficient to rupture that of a normal subject The ordinary tourniquet test of Rumpel and Leede increases the intravascular pressure above physiologic values while Dalldorf s suction method reduces the extravascular pressure to levels lower than atmospheric either technic is suitable Correlation between capillary fragility and chemical assay of ascorbic acid saturation is however far from close Since scurvy represents by definition the effect of ascorbic acid depletion this discrepancy suggests the possibility that capillary resistance may be dominated by some food factor other than vitamin C—Szent Györgyi s P substance perhaps The use of capillary fragility tests to support the diagnosis of scurvy

must be tempered by a full appreciation of their lack of specificity

Biochemical assay of the ascorbic acid stores has come to play a salient part in diagnosis especially in those cases in which the deficiency falls short of evoking characteristic physical signs of scurvy A plasma level close to zero accompanies all cases of untreated scurvy but identical values may be found in many subjects who are symptom free and who in consequence cannot in all truth be described as scorbutic The same may be said of low urinary concentrations Accurate evaluation of the degree of depletion may be achieved in any of three ways (1) simultaneous determination of the concentration of ascorbic acid in the patient s plasma and in the white cell and platelet layer of centrifuged blood (2) measurement of the plasma level in the fasting state and after intravenous or intramuscular administration of a test load of ascorbic acid (3) daily estimation of the total urinary excretion of ascorbic acid for several days following liberal dosage of the vitamin (of the order of 500 mg daily) Depleted stores are indicated in (1) by low values in both determinations in (2) by a low flat four hour curve in (3) by a delay of two days or more in the rise of urinary excretion

Since the response of a scorbutic patient to specific antiscorbutic therapy is usually prompt and dramatic and since the vitamin is available not only in the pure state but also conveniently in high concentration in orange juice and other vegetable sources the use of a simple therapeutic diagnostic test is legitimate and often decisive This makes it possible to explore a presumption of scurvy without the aid of accessory equipment and in favorable circumstances to lend strong probability to the diagnosis of scurvy once it has been taken into consideration It is when scurvy is not even thought of in the differential diagnosis that it is wrongly labeled as rheumatism myositis purpura or neurasthenia

Prognosis —Scurvy is readily amenable to treatment provided it be recognized in time and the prognosis generally depends on the complications—particularly on the infections—which the disorder has permitted to gain a foothold Of these tuberculosis is most to be feared Conspicuous as is the tendency to hemorrhage in the symptomatology of the disease fatal bleeding is rare unless as a result of surgical intervention from drainage of an infected hematoma or from the mistaking of a subperiosteal hemorrhage for osteomyelitis Under ordinary conditions of civil life deaths from uncomplicated scurvy are almost unknown

The deformities which accompany severe epiphyseal infractions in infantile scurvy are not of ultimate importance even though the healing process may cause the fragments to fuse in positions of faulty alignment, for with the resumption of normal growth the bone eventually attains anatomic as well as functional integrity

Treatment —The optimal intake of vitamin C for the normal subject has yet to be determined, dietitians argue that anything less than a state of repletion of the stores compromises the body s economy, but historic and general clinical evidence suggests that moderate unsaturation is not inconsistent with physiologic efficiency In a therapeutic test for diagnostic purposes the daily administration of 250 mg of ascorbic acid or about 16 ounces of fresh orange juice may be expected to dispel anorexia relieve mental depression to a considerable degree eliminate tenderness of the extremities and obviate the appearance of fresh capillary hemorrhages within from two days to a week provided these symptoms have their origin in a deficiency of vitamin C The total quantity of ascorbic acid required to re saturate a scorbutic patient varies from about 2 Gm up to ten or more times that amount differences depending in part on superior efficiency of vigorous dosage in the early stages of therapy as compared with smaller daily dosage over a more protracted period Absorption of orally administered ascorbic acid is usually complete or nearly so appreciable reduction in absorption occurring only in the presence of diarrhea or chronic disease of the intestinal tract Solutions of ascorbic acid are well tolerated in the blood stream as much as 6 Gm having been given in a single dose without adverse effect In spite of its acidity a 1 or 2 per cent solution of ascorbic acid in normal saline need not be buffered nor neutralized for intravenous injection

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RICKETS

Definition—Rickets is a disease characterized chiefly by clinical and roentgenologic abnormalities of the skeleton which result from deficient deposition of lime salts in growing cartilage and in newly formed bone Except in rare instances to be enumerated later it is a deficiency disease which is caused by insufficient vitamin D during the age when growth is rapid Since the human organism is able to supply its need for the vitamin either by ingestion or by autosynthesis in the presence of a form of radiant energy contained in sunlight rickets is an expression of the combined absence of two factors one dietetic and the other environmental

Incidence—Since rickets is intimately related to the velocity of growth the disease primarily affects infants at the age when rapid growth is taking place Several months must usually elapse before the manifestations are perceptible clinically the disease is therefore rare in the early weeks of life and the majority of cases are diagnosed between the ages of four months and two years Under exceptional circumstances as when the mother suffers from a form of osteomalacia which results from lack of vitamin D Maxwell has shown that the disorder may exist at birth In the absence of prophylactic measures the incidence is extremely high during the susceptible age period The highest estimate is that of Schmorl who drew his conclusions from autopsies in Dresden between 1901 and 1905 94 to 98 per cent of infants between the ages of four months and one and one half years exhibited the disease A similar recent study by Park and Eliot in Baltimore indicated an incidence between 44 and 60 per cent between the ages of seven months and two years By means of x ray films Eliot and Souther investigated 1186 healthy children of mixed stock in New Haven The incidence of rickets of moderate or marked severity increased from the third month to a peak of 24 per cent at eighteen months and then declined to about 5 per cent at the third year Mild rickets which was demonstrated only by x ray affected 35 per cent of the infants between three and six months of age Combined incidence of mild and more advanced rickets at this early age period was about 50 per cent It is interesting to note that the occurrence of mild rickets coincides closely with the period of most rapid growth and that antirachitic measures are considerably less effective in removing the milder manifestations than in eliminating advanced rickets The question has therefore been raised as to whether mild rickets may not represent a physiologic manifestation of growth

The premature infant is particularly susceptible to the development of rickets The susceptibility is so extreme that one is almost justified in saying that moderate or severe rickets will develop in all premature infants unless preventive measures are instituted Twins belong in the same category

Rickets is predominantly a disorder of the temperate zone It is extremely rare in the far north where fish constitute the chief source of food the influence of sunlight prevents its occurrence in the tropics There is a striking seasonal incidence in the northern hemisphere the peak occurs during the winter and spring months when the rays of sun from the south are slanting Environmental variations in the amount of exposure to the sun also account for a greater prevalence in urban than in rural communities It is well known that the Negroes and Italians who dwell in the cities of the United States are unusually susceptible to rickets the susceptibility is accounted for at least in part by the dark pigmentation of the skin which offers a barrier to the penetration of radiant energy

Pathology—There are few diseases of which it is more true than of rickets that a knowledge of the pathology will bring an almost complete understanding of the clinical and roentgenographic manifestations The distinctive findings are limited to the skeleton and result chiefly from the failure of lime salts to be deposited in growing cartilage and in newly formed bone The uncalcified bone or osteoid tissue is morphologically similar to normal bone but because it lacks the elements essential for rigidity it is soft and easily distorted In health the formation of new bone is greatest at the ends of the long bones and at the costochondral junctions in these places rickets produces the greatest change Calcification about the proliferating cartilage cells fails capillaries from the shaft finding no supporting framework to guide the direction of their growth invade the region between cartilage cells and carry with them an envelope of connective tissue The cartilage cells failing to be destroyed by the normal process of metaplasia persist in scattered tonguelike aggregations which reach out from the cartilage into the shaft Thus the regular epiphyseal line of health disappears and in its place there develops a zone of varying width composed of osteoid and connective tissues blood vessels and cartilage cells This is the rachitic metaphysis The amount of calcified tissue which remains in the zone varies inversely with the severity of the rickets the width of the zone is roughly a measure of the duration of the disease The scattered lime salt deposits can be visualized in x ray films and give rise to the characteristic rachitic fringe at the ends of the bones The rachitic metaphysis is soft and in response to external stress the bone will bend in this region The constant pull of muscles and tendons tends to mushroom the firm epiphyseal cartilage into the metaphysis The resulting increase in circumference is the epiphyseal enlargement of rickets the hollowing out of the central portion of the metaphysis is responsible for the cup shaped deformity in x ray films Although the effect of rickets is most marked at the ends of the bones evidence of the disorder is also found in the shafts In healthy bone the process of destruction by osteoclasts and replacement by osteoblasts is continuous in rickets the process is similar except that replacement is by osteoid rather than by osseous tissue Trabeculae of bone come to be enveloped by *a mantle of osteoid tissue* as the disease continues the thickness of the mantle grows and the diameter of the bony core decreases Fractures are frequently found In x ray films the entire shaft appears rarefied This osteoporosis of rickets differs from that of disuse or of scurvy in that the trabeculae are not diminished in size and that the degree of penetration by x rays is determined solely by their lime salt content In health the production of cortical bone is a function of the periosteum In rickets the periosteum is sometimes excessively active in laying down concentric layers of lime deficient bone so that the shaft becomes considerably increased in thickness It is as though nature were attempting to compensate for the structural weakness

When under the influence of an antirachitic agent the rickets begins to heal the first demonstrable evidence of change results from calcification of the matrix about the more recently differentiated cartilage cells The new epiphyseal line which is formed is demonstrable by x ray and at once demarcates the distal end of the rachitic metaphysis The hiatus which remains between the new line and the shaft is obliterated more slowly as are also the signs of disease in the shaft itself

Etiology, Metabolic and Chemical Aspects—The changes in the bones in rickets are undoubtedly the result of a general disturbance in the metabolism of calcium and phosphorus The concentration in the serum of either one or both of these elements is always below normal while the rachitic process is advancing That this deficit in the serum is the chief cause of the skeletal lesions is shown by the fact that calcification of the intercartilaginous matrix of rachitic bone can be induced *in vitro* when a slice of the freshly excised tissue is immersed in normal serum The serum of healthy infants normally contains per 100 cc 10 to 11 mg of calcium and 4 5 to 5.5 mg of inorganic phosphorus According to Howland and Kramer the product of the calcium and phosphorus when both are expressed in milligrams per 100 cc furnishes an index of the presence or absence of rickets A product

less than 30 indicates the presence of rickets a product between 30 and 40 may or may not be associated with rickets a product greater than 40 indicates either that rickets is absent or that the disease is undergoing healing Although the practical value of the product is generally recognized Park has stressed the necessity of considering the rate of growth as an additional variable In most cases of rickets the serum calcium remains normal and the inorganic phosphorus alone is low When rickets is associated with tetany the calcium level is affected chiefly though both elements may sometimes contribute equally to the disturbance

The mechanism which controls the level of lime salts in the blood is not well understood although some facts about it are known Metabolism experiments have demonstrated that vitamin D has a profound effect on the absorption of these salts from the intestine During rickets the greater part of the ingested calcium and phosphorus is excreted in the stool even though the loss is rarely great enough to produce an actually negative balance With healing a strongly positive balance is established until the depleted skeleton has been replenished Thereafter the larger part of the excess phosphorus over that required for growth is excreted in the urine while the bowel continues to be the principal route for eliminating calcium That faulty functioning of the parathyroid glands plays a part in producing the abnormal blood findings in rickets is also highly probable These glands are hypertrophied in rickets the effect of the specific hormone in raising the level of calcium in the serum is well known

In rare instances rickets may be caused by disturbances which are unrelated to an inadequate supply of vitamin D The primary defect responsible for so called refractory rickets is not known Nevertheless success in therapy may follow the administration of vitamin D in doses which are many times as large as those commonly employed in the treatment of severe privational rickets Chronic renal insufficiency may be associated with rickets Apparently failure of the kidney to excrete phosphorus leads to the passage of this element into the bowel where it interferes with the absorption of calcium Hypocalcemia ensues and is followed by hypertrophy and hyperactivity of the parathyroid glands The excess of parathormone is responsible for the demineralization of bone In another rare type of rickets the disorder is associated with glycosuria and an excessive excretion of organic acids in the urine In other similar cases the urinary excretion of glucose is not observed and the process is attended by widespread deposits of cystine crystals throughout the cells of the reticulo endothelial system and occasionally by the excretion of cystine in the urine

Symptoms and Physical Signs—The accuracy which the x ray has contributed to the diagnosis of rickets has rendered it clear that the only characteristic signs are those which pertain to the skeleton Other manifestations such as irritability excessive sweating or muscular hypotonia are either difficult to evaluate or common to so many disorders as to be of no aid in recognizing the disease As a single exception the manifestations of tetany during infancy strongly suggest the presence of rickets Tetany however is a complex of symptoms which accompanies only a small fraction of all cases of rickets and which may occur occasionally from causes other than those responsible for rickets The skeletal signs of rickets are the combined result of the softened state of bone in the regions where growth is occurring and of the external stresses to which these regions are exposed Since age is a factor in determining the sites of rapid growth and since new stresses come into play when the child learns to sit and to stand it is apparent that the manifestations of rickets must vary in relation to the age at which they develop Long after the disease has ceased to be active the residual deformities are evidence of the age at which the process was most intense

Craniotabes may be the earliest demonstrable sign of rickets it is rare after the eighth or ninth month of life It develops in the occipital or parietal bones in one or more areas removed from the lambdoidal suture and invariably on that side of the head upon which the infant has habitually lain It is usually associated with softening along the suture line Craniotabes is often overlooked on routine physical examination its presence is detected by pressure with the

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chondrium and periosteum Another type of bony enlargement may result from excessive production of subperiosteal bone In the hands it leads to fusiform enlargement of the proximal and middle phalanges (*string of pearls* deformity)

Most conspicuous among the permanent malformations caused by rickets are the *bending* deformities To a large extent they originate when the disease continues to be active after the child has learned to sit The rachitic child shows little inclination to engage in the incessant activity which characterizes his healthy peers a posture once chosen becomes habitual and he sits for hours in essentially the same position The resulting stress on the skeleton leads to deformity not only because the bones are unusually yielding but also because the direction of application is unusually constant Commonly the child sits with thighs slightly spread apart and with one lower leg crossed over the other the hands are placed on the floor or on the thighs to assist the spine in holding the trunk erect The pull of gravity on the foot is augmented by that of the Achilles tendon so that the lower epiphyses of the tibia and fibula are displaced backward producing an angular deformity (*saber shin*) At the time of its origin the maximal convexity is just above the ankle With increasing age the bones grow in length beyond this site and ultimately the greatest bend is about one third the way up the shaft of the tibia Stress on the femur from the same posture leads to lateral and forward bowing and the femoral head is bent forward toward the shaft (*coxa vara*) That portion of the spine which is unsupported by the thorax is unusually vulnerable and marked lumbar kyphosis is not uncommon The combined deformities of lumbar kyphosis pot belly and flattened thorax produce a striking picture when the child is viewed in profile the outline is that of an erect truncated cone with the base at the level of the navel Less conspicuous bending deformities may develop in the upper extremities The humerus bows outward and the lower epiphyses of the radius and ulna may be bent to one side or the other depending upon the direction in which the hands are habitually turned When the child with rickets has learned to stand the stresses are altered Kyphosis is replaced by lumbar lordosis coxa vara is increased, and bowlegs or knock knees make their appearance The significant rachitic flattening of the pelvis probably begins during infancy from the force of gravity and is increased by the stresses applied during sitting and standing

Rickets leads to delayed eruption of the temporary teeth and is also associated with defects in calcification of the unerupted permanent teeth These defects are permanent and later appear as irregularities in the surface structure (*enamel hypoplasia*) Such teeth because of their defective structure are particularly prone to caries However it has not been demonstrated that an immediate relationship exists between vitamin D deficiency and dental caries

Diagnosis by X ray —The prevalent use of x rays has brought increased certainty to the early diagnosis of rickets and has provided the most satisfactory way of following the effect of therapy Much of our present knowledge would be lacking without them It is true that the very earliest signs of rickets which appear at the costochondral junctions cannot for technical reasons be visualized in roentgenograms but it is also true that clinical appraisal of departure from normal form in the rib cartilage junction is even more difficult A common clinical error is to diagnose rickets when no rickets is present

Experience has shown that the x ray changes characteristic of rickets are most easily recognized in pictures of the lower ends of the radius and ulna taken with the arm in complete supination The earliest changes are seen almost exclusively at the cartilage shaft junction The normally sharp termination of the shaft becomes blurred and finely irregular (*fraying*) the line of termination tends to become concave (*cupping*) the end of the bone is widened (*spreading*) and in some instances *cortical spurs* may be present at the lateral margins where lime salts have been deposited in the perichondrium which is adjacent to the periosteum Visualization of the very early changes depends upon faultless technic in making the pictures it is necessary to be sure that fraying has not arisen from slight movement on the part of the patient As the disease progresses to the moderate and

finger over the probable sites of involvement and the finding of relatively soft areas where the skull buckles and snaps back when the pressure is released The sensation is much the same as one experiences when pressing on the crown of a derby hat As the infant approaches the end of the first year of life craniotabes generally disappears even though the rickets continues to be active By this time however, the skull may present other evidence of the disease The eminences of the frontal and parietal bones become unusually prominent later are thickened into actual bosses which produce a square head (*caput quadratum*) Sometimes the eminences stand out as four rounded elevations separated by depressions which mark the lines of sultures (*hot cross bun* head *caput natiforme*) Rickets also results in delayed closure of the fontanels In severe cases the anterior fontanel may still be membranous at the age of three or four years



Fig 48—A rachitic child twenty months of age

Thoracic deformities belong among the early signs of rickets Rapid growth of the ribs during infancy renders the costochondral junctions particularly the sixth and seventh unusually susceptible Here rounded enlargements make their appearance and can be palpated along a line which extends downward and laterally on either side of the chest This is the *rachitic rosary* As the disease progresses the weakened metaphyses of the ribs yield to the force of negative pressure in the thorax and bend inward When the enlargments at the rib cartilage junctions are palpable externally they are even more prominent on the inner wall of the thorax Finally an external groove or depression develops along the line of the rosary At its lower end the groove merges with a girdle like depression (*Harrison's groove*) which appears when the ribs have bent inward along the attachments of the diaphragm Harrison's groove is generally accentuated by flaring of the lower ribs and distention of the abdomen Park and Howland have pointed out that the functional embarrassment which attends severe rickets of the thorax may actually endanger life The thoracic cage instead of expanding with each downward excursion of the diaphragm may even become more constricted pulmonary ventilation is further reduced by wide areas of atelectasis respiration is rapid and difficult and a relatively mild infection may have a fatal termination

Enlargements at other epiphyses develop more slowly than at the costochondral junctions but are often well developed before the end of the first year of life They are recognized most easily at the wrists and ankles where the subcutaneous tissue is relatively thin When the swelling is slight it is difficult to be sure that one is not dealing with the normal protuberances of the malleoli or styloid processes In examining the wrist the writer has made it a practice to palpate the dorsal as well as the lateral aspects since an abnormal swelling at the former surface is less liable to be confused with normal styloid processes Marked enlargement is now and again associated with an additional sign of abnormality namely *apparent duplication of the epiphysis* The sign is most conspicuous at the ankle where particularly the external but sometimes also the internal malleolus presents a double rather than a simple hump at the maximal convexity A pathologic specimen in the author's possession indicates that the lower or distal hump is caused by cartilage surrounding the nucleus of ossification and the upper or proximal hump by rachitic metaphysis that is there is a groove around the bone which marks the junction of peri

units per quart irradiated fresh milk and reconstituted irradiated evaporated milk furnish about 135 units per quart Since the average consumption of milk by an infant is less than a quart a day, the question is raised as to whether the lower dosages of vitamin are sufficient for prophylaxis Until experience has been amplified a final answer is impossible However it appears clear that the administration of any of the milks to full term infants is ample prophylaxis against the more severe types of rickets Milks which furnish 400 or more units per quart would seem to be as effective as the usual prophylactic dose of cod liver oil milks which provide only 135 units per quart allow the development of moderate rickets in enough instances to prevent complete confidence in their prophylactic efficiency

Although most cases of active rickets will respond satisfactorily to treatment with cod liver oil the time required for cure can be much shortened when one of the more powerful antirachitic agents is employed It is not practical to administer more than three teaspoonfuls of cod liver oil daily to an infant Viosterol is preferably prescribed in doses of from 4000 to 10 000 units daily (twenty to fifty drops of the official solutions) according to the severity of the disease This amount should be continued for two to three months and only slowly reduced to the usual prophylactic amounts When ever possible the effectiveness of treatment should be followed by serial x ray films taken at first at intervals of two or three weeks

Finally the prevention of rickets in the premature infant presents a special problem The unusual susceptibility of these patients renders large doses of vitamin necessary for adequate prophylaxis A satisfactory routine is to start with five drops of viosterol daily at the age of two weeks and increase the dosage by five drops at weekly intervals until thirty drops daily is being administered This level should be continued until the infant is seven or eight months of age when it may be replaced by the usual prophylactic regime

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PELLAGRA

Definition —Pellagra is a noncontagious nonhereditary clinical syndrome affecting the skin alimentary tract and nervous system It is characterized by seasonal recurrences and relapses and may occur in any race and at any age

History—The term "pellagra" from the Italian pelle agra" meaning rough skin was first used in medical literature in 1771 by the Italian physician Frapolli who found the word in common use among the peasant population of Lombardy The authentic history of the disease begins somewhat earlier in northern Spain In the year 1735 Gaspar Casal, physician to King Philip V recorded his observations on mal de la rosa, a malady prevalent among the peasantry in the province of Asturias Twenty years later Antonio Pujati reported its presence in northern Italy and in 1784 a special hospital for the treatment of pellagrins was established at Legano by warrant of Joseph II of Austria During the nineteenth century the disease was observed in many other countries chiefly in France Egypt and Roumania In the United States of America, sporadic cases had been reported as early as 1864 from New York and Massachusetts but it was not until 1907 when Searcy called attention to the presence of a large number of cases of endemic pellagra in an asylum in Alabama that the seriousness of the situation in the southern part of the United States was appreciated Within the next few years many cases were reported from practically all southern and from many northern States

Incidence —Pellagra occurs in every country The incidence is high in Egypt United States of America Roumania Serbia Bulgaria Russia Italy and Spain Professor W H Wilson estimates that 30 per cent of the population of Egypt are affected with pellagra and the United States Public Health Service estimates that there are 400 000 cases annually in the United States of Amer

more severe stages the alterations become unmistakable The spreading increases the end of the shaft is hollowed out into a crater and the fraying widens into a fringe which may be 1 cm or more in width The visual izable evidence of disorder depends upon irregularly scattered areas of calcification throughout the rachitic metaphysis in the most severe form of rickets when calcification has ceased entirely the changes may be absent and the shaft appear to end abruptly as before the disease began In such cases the onset of healing is marked by the sudden appearance of all the characteristic features Severe rickets is also attended by equally distinctive x ray findings in the shaft These include marked osteoporosis either thinning or sometimes a lamellated type of thickening of the cortex and cloaking of the shaft with rarefied subperiosteal bone Change in the shaft however is rarely useful in establishing an early diagnosis and is a less sensitive index of the progress of successful therapy than is the cartilage shaft junction

The beginning of healing is heralded in x rays by the appearance of new deposits of lime salts in the zone between bone and cartilage Particularly prominent is the reappearance of an epiphyseal line at the proximal boundary of the cartilage At this stage the end of the bone is marked by two horizontal lines between which the area of greatest disorder is isolated The final obliteration of signs of the disease in x ray films may require many months

Prophylaxis and Treatment —The number of agents available for the prevention and cure of rickets has been increasing with bewildering rapidity The list now includes exposure to sunlight or to artificially produced ultraviolet light cod liver oil halibut liver (haliver) oil percomorph liver oil from an order of fishes which includes the tuna the swordfish the red snapper and the California sea bass viosterol concentrate of the nonsaponifiable fraction of cod liver oil crystalline vitamin D dissolved in propylene glycol and several types of antirachitic milk in which activation is accomplished by the inclusion of irradiated ergosterol in the diets of the cows (metabolized or yeast milk) by direct irradiation of the milk (irradiated milk) or by adding to the milk a homogenized concentrate of cod liver oil (vitex milk) All of these agents appear to be effective when given in adequate dosage they differ greatly in concentration of vitamin D in cost per unit of vitamin and in their associated content of vitamin A The list of agents is augmented by the availability of mixtures of the more potent remedies with cod liver oil These include cod liver oil with viosterol cod halibut liver oil and cod liver oil with percomorph liver oil

The student will avoid confusion if he remembers that the experience of clinicians regarding adequate dosage is far greater with cod liver oil than with any of the other preparations This experience has shown that a daily dosage of three teaspoonfuls of cod liver oil of average strength is sufficient to prevent rickets in the vast majority of infants Administration is begun in smaller dosage at the age of two or three weeks and increased slowly to the level mentioned The minimum U S P requirement for cod liver oil is a potency of 85 international (or U S P) units per gram the average cod liver oil on the market contains about 100 units per gram Three teaspoonfuls of this oil furnish about 1200 units This figure can be remembered as a rough guide in gauging the amounts of other antirachitic agents to be prescribed Several special brands of cod liver oil are available which are considerably more potent than the average article for instance that marketed by one firm contains 175 units per Gm The preventive dose of these special brands of oil is in the neighborhood of two teaspoonfuls per day Under particular circumstances the physician may wish to prescribe one of the more potent remedies for prophylactic purposes The official viosterol in oil contains 10 000 units per Gm or about 200 units per drop and the desired dosage is easily calculated In general however cod liver oil answers the need for an effective prophylactic agent and has the advantage both of being an excellent food and of supplying considerable amounts of vitamin A

A word must be added concerning the prophylactic value of the antirachitic milks As now marketed yeast milk contains about 435 units per quart milk with added concentrate of cod liver oil furnishes about 400

Prodromal Symptoms—The onset of pellagra is often so gradual that the earliest symptoms may not be noticed by the patient Early in the disease there is a loss of strength particularly in the legs a change in appetite and usually though not always a decrease in body weight There may be also a change in mood or in personality Pellagra in the early stages of the disease is often incorrectly diagnosed as neurasthenia

Skin—Pellagrous dermatitis is not always present but when observed may be readily diagnosed by its appearance symmetry, location and course Symmetric lesions may appear on any portion of the body, but are most common over sites of irritation such as the hands wrists elbows neck under the breasts knees feet and in the perineal region A sharp line of demarcation at the periphery of the lesion separates the affected area from the healthy skin In the majority of cases pellagrous dermatitis is restricted to the exposed parts of the body and the dermal lesions of pellagra often appear following exposure to sunlight The dermatitis begins as an erythema resembling sunburn As the disease progresses the area becomes reddish brown roughened scaly and keratotic vesicles and bullae may form Desquamation usually begins at the center of the lesion and the underlying skin appears red and thickened The intensity of the pigmentation and the thickening of the skin tend to increase with each recurrence of the disease after repeated recurrences the skin may become either permanently pigmented thick and roughened or thin and atrophic

Alimentary Tract—Both glossitis and stomatitis are early and common symptoms and are usually of such character as to be diagnostic of the disease In the beginning only the tip and lateral margins of the tongue are swollen and reddened If treatment is not given the swelling increases the red discoloration becomes more intense and deeply penetrating ulcers may appear along the sides and tip—rarely on top Frequently a thick gray membrane filled with debris and Vincent s organisms covers the surface The tongue is usually hypesthetic though it may be hypersensitive The buccal membranes the mucocutaneous surface of the lips the gums and the palate may likewise be affected The course of the stomatitis is similar to that of the glossitis A burning sensation of the tongue and of the mucous membranes of the pharynx esophagus and stomach is not uncommon this is often aggravated by hot or acid foods Ptyalism, nausea and vomiting may occur early but as a rule these are advanced symptoms of the disease About 50 per cent of pellagrins have no free hydrochloric acid even after histamine stimulation rennin and pepsinogen are likewise absent This achylia gastrica tends to persist during remissions The stools may be hard soft or watery but the odor is invariably foul Contrary to what is generally taught the bowels in the majority of mild cases act normally or are constipated Severe persistent diarrhea with several watery stools each hour tends to appear only in the more acute cases Abdominal distention discomfort and pain may be present at any time during the course of



Fig 49—Symmetric exfoliating lesions on elbows and dorsal surface of the hands of a pellagrin in relapse Multiple areas of ulceration and a few large bullae can be seen

ica It is believed that at least 10 per cent of the inmates of the insane asylums in the southern part of the United States were admitted because of pellagra

Etiology —For many years opinion in regard to the cause of pellagra was divided The two prevailing theories were (1) that it was a dietary deficiency disease and (2) that it was an infection in which diet played a more or less important role The spectacular improvement in so many pellagrins who receive intensive dietary treatment leaves no doubt that the disease may be explained on the basis of a dietary deficiency At the present time the consensus of opinion among investigators is that pellagra is a clinical syndrome caused primarily by a nutritional deficiency which may arise in one or more of the following ways (1) The person s diet may be inadequate in the antipellagric foods (2) His absorption may be impaired because of altered gastro intestinal function (3) His requirement for the antipellagric substances may be in excess of the amount supplied by a liberal well balanced diet

Goldberger advanced the theory that the pellagra preventive factor is a single substance vitamin B_2 (G) the thermostable portion of the vitamin B complex and until recently many students of nutrition accepted this theory It is now known that vitamin B_2 is not a single substance but is composed of a number of active principles Three of these namely nicotinic acid riboflavin and pyridoxine have been synthesized and thus far they are the only ones which have been found to play a role in human nutrition It has been shown that nicotinic acid is a specific curative agent for the mucous membrane lesions for many of the symptoms arising from the alimentary tract and for the mental symptoms of human pellagra and that it aids in preventing recurrences of these symptoms Its relationship to the dermatitis of pellagra has not been fully established Following the administration of nicotinic acid the concentration of cozymase and coferment (coenzymes I and II) in the blood and urine of pellagrins is increased from subnormal to normal values The increase in concentration of these coenzymes which are fundamental to cell respiration parallels the clinical improvement of the patient

Certain predisposing and precipitating factors often play a role in the pathogenesis of the disease Important among these are fatigue insomnia loss of teeth infections food idiosyncrasies, chronic alcoholism and diseases which cause improper ingestion assimilation or utilization of food Failure to consider all of the above mentioned conditions as underlying factors in the cause of pellagra has led to the designation of certain cases as pseudo pellagra ' pellagra sine pellagra postalcoholic dermatitis alcoholic pellagra and secondary pellagra Such terms are confusing and should be abandoned the disease is or is not pellagra

During the past twelve years from the study of over 10 000 pellagrins we have found that the inadequate diets of these persons predispose them simultaneously to a number of nutritional deficiencies and that pellagra frequently coexists with beriberi and riboflavin deficiency The diagnosis of pellagra therefore necessitates a thorough search for evidence of other deficiency syndromes and the institution of therapy specific for each deficiency

Morbid Anatomy —The most common gross findings are generalized emaciation of the body and atrophy of various organs Pellagra can be diagnosed at the postmortem table only when the characteristic oral and skin lesions persist In some cases the walls of the gastro intestinal tract may show swelling reddening and ulceration of any portion while in other cases the walls may be thin and atrophic The liver occasionally contains abnormal amounts of fat *Histologically* the skin lesions vary from atrophy to an intensive inflammatory reaction Similarly the microscopic picture of the intestinal lesions varies from atrophy to acute inflammation characterized by fibrin formation and collections of inflammatory cells When changes in the nervous system are demonstrable they are characterized by irregular areas of degeneration often involving the posterior and lateral columns of the spinal cord the posterior spinal ganglia and the Betz and Purkinje cells

Symptoms —These arise chiefly from the skin gastro intestinal tract and nervous system They vary greatly with each patient arising in some from only one of the systems and in others from two or more

the daily life of the patient must be properly regulated or he will fail to make satisfactory progress Without special treatment the death rate is more than 50 per cent in the severe cases Once the disease mild or severe has remitted *the prognosis is good* if no other predisposing condition or organic disease is present and provided the patient is cooperative and has perseverance and the capacity to continue treatment

Pellagrins who seem to be making satisfactory progress often become suddenly worse and die No single manifestation can be used as the sole indicator of the prognosis *In each case the immediate outlook is contingent* upon the general condition of the pellagrin and upon the presence or absence of other diseases

The outlook is most grave when severe mental symptoms hallucinations, violent motor excitement opisthotonos delirium rigidity tremors ankle clonus Babinski s sign or convulsions are present Extensive *and severe gastro-intestinal symptoms such* as intractable diarrhea and vomiting severe glossitis stomatitis and cachexia may also have an unfavorable effect on the course of the disease Refusal of food long continued abdominal distention and marked anemia should be regarded as ominous signs Pellagra is not usually accompanied by fever a temperature of 103° F makes for an unfavorable *prognosis The danger is increased if* chronic addiction to alcohol fatigue or surgical operations intervene The presence of infection darkens the outlook for just as infectious diseases predispose to pellagra so are pellagrins unusually susceptible to infections

Prevention —Pellagra can be prevented by the intelligent application of medical knowledge In order to eradicate pellagra people with organic disease those who are poor chronic alcohol addicts food faddists and those with improper dietary habits must receive special attention

Organic Disease —Organic disease often predisposes to pellagra by affecting the general nutrition and probably by increasing susceptibility Particular attention to the diet while the disease is being treated prevents the development of pellagra The incidence of pellagra is abnormally high among people having metabolic diseases chronic infections and diseases of the gastro intestinal tract

Poverty —Although pellagra often develops as the result of financial inability to buy proper food lack of knowledge in regard to *diet is an important contributing factor* If sufficient amounts of a well balanced diet are eaten regularly, pellagra will not develop Education of the poor in correct dietary habits is indicated so that those who can but do not may buy the inexpensive protective foods and those who cannot afford them may obtain protective substances such as yeast and wheat germ *through relief agencies*

Chronic Alcoholism —Chronic alcoholic addicts who do not eat adequate amounts of a well balanced diet develop pellagra Alcohol alone does not cause the disease but it often decreases the patient s appetite and diminishes his food intake This is easily understood when we consider that often the heavy drinker receives from 3000 to 4000 *calories per day from the alcohol alone* When alcoholic pellagrins are induced to stop drinking their appetites return they eat more food the disease is arrested and is not likely to recur Likewise alcoholic pellagrins who can be persuaded to eat large amounts of food do not have recurrences

Improper Dietary Habits —It is a popular fallacy to believe that our customary diets *are adequate Many people live on a diet* of narrow range too high in fats and carbohydrates because of custom preconceived ideas as to what foods are good for one and dependence upon the appetite as the guide in the proper selection of foods Education of the masses in the essential dietary requirements is imperative

Treatment —Pellagra is a systemic disease and must be treated as such early promptly intensively and persistently The essence of successful treatment is improved nutrition adequate rest and good medical and nursing care The methods must be adapted to the special needs of each patient and can be carried out most effectively if the patient is hospitalized and placed under the direct supervision of a doctor assisted by a nurse and a dietitian

Treatment of the Mild Case —Every adult with mild pellagra must ingest and retain a well balanced high protein diet of

the disease but are more severe after a large meal

Nervous System—Nervous symptoms are common but at the onset of the disease are often vague and ill defined The patient may complain of nervousness insomnia head aches dizziness muscular weakness and a bilateral burning of the hands feet and other parts of the body The tendon reflexes are frequently altered At first they may be exaggerated later decreased finally they may be absent The extremities particularly the legs may feel numb or become paralyzed Typical subacute combined de



Fig 50—Photograph showing symmetric dry scaly pellagrous dermatitis on the feet of a Negro Note the sharply demarcated borders and the hyperpigmentation at the periphery of the lesions

generation of the spinal cord with spasticity and ataxia is found Tremor and a spastic or ataxic gait is often associated with peripheral neuritis in the advanced cases

Mental Changes—Pellagrins are subject to periods of depression and apprehension and unless treatment is administered hallucinations confusion delirium and complete disorientation may develop Tremor jerky movements and rigidity of the body frequently accompany these mental symptoms If such cases are given early and intensive treatment the mental symptoms seldom persist but in the absence of treatment the patient is likely to become insane

Organs of Special Sense—Any of the organs of special sense may be affected, loss of taste and smell are common

Genito-urinary System—Burning on urination occurs frequently Libido is often decreased sterility is unlikely In the female acute pellagrous vaginitis with Vincent's infection is a usual finding Menstruation may be scanty or absent

Circulatory System—In the mild case a slightly subnormal blood pressure is often noted In the severe case there is an increased pulse rate lowered blood pressure and vasomotor collapse Syncope and sudden death frequently occur

Blood—The hemoglobin is less than 70 per cent in the majority of patients with severe pellagra The anemia is either macrocytic or microcytic in type

Temperature—The temperature of the mild uncomplicated case is usually normal an elevation of several degrees is serious as it denotes the presence of an infection or a severe type of the disease

Diagnosis—The typical case is easily diagnosed on the basis of a reliable history and careful physical examination The history is usually one of an inadequate or unbalanced diet high in carbohydrate and fat content Physical examination reveals the characteristic dermal and lingual lesions Atypical cases are many and can be recognized only by careful clinical study as there is no specific laboratory test for pellagra Were it not for the skin and oral changes characteristic of pellagra neither the typical nor the borderline cases could be distinguished from cases of chronic alcoholism beriberi pernicious anemia or sprue

Prognosis—Pellagra is always a serious disease A favorable course depends on an early diagnosis followed immediately by intensive and persistent treatment If untreated or incompletely treated it usually becomes chronic and continues through remissions and recurrences until either the pellagra itself or a coexistent or resultant secondary disease produces incapacitation or death The disease tends to increase in severity with each attack but the author has observed recovery after thirteen distinct relapses Even in cases with rare recurrences

PERIPHERAL NEURITIS —Ice bags and local medications containing phenol (1 per cent) and menthol afford temporary relief Physical therapy and splints are often beneficial For use of vitamin B_1 see Beriberi

TOM D SPIES

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BERIBERI

Definition—Beriberi is a clinical syndrome associated etiologically with a faulty food supply or an alteration of metabolism It is characterized clinically by multiple neuritis serous effusions edema muscular atrophy and cardiovascular changes Without being contagious it occurs sporadically and endemically and passes in great waves over the Oriental countries The disease is associated with ignorance and poverty and may appear in any race and at any age It is prevalent among infants whose mothers have beriberi

History.—Though the precise origin of the word beriberi is unknown the term undoubtedly arose from an Oriental language many centuries ago There is good reason to believe that the disease was described in the Neiching (2697 B C) Subsequent literature of the East contains many references to beriberi or to a disease so similar that it cannot be distinguished from it In 1642 Jacobus Bontius the first Occidental physician to describe the disease pointed out that the natives of Java called it beriberi During the nineteenth and twentieth centuries great interest arose in the recognition and prevention of beriberi and closely related diseases During this period of renewed clinical interest investigators applied dietary methods of prevention to special groups of the population with great success

Incidence—Beriberi occurs sporadically throughout the world It is prevalent both among infants and adults in the endemic areas of China Japan the Dutch East Indies Brazil India the Malay Peninsula and the Philippine Islands At times sudden outbreaks of the disease occur in these countries and in prisons and asylums of the Western World

For many years it was believed that beriberi seldom occurred in the Western Hemisphere Recent studies show however that beriberi (nutritional peripheral neuritis) is much more prevalent than is commonly supposed Its incidence is high among pellagrins alcoholic addicts and pregnant women It is frequently associated with organic disease and often coexists with other nutritional deficiencies

Etiology.—The results of clinical and experimental studies point to a definite relationship between an unbalanced diet abundant in decorticated cereals and the development of beriberi Such diets are known to be deficient in vitamin B_1 Although it has not been proved that one specific factor is the sole cause of the disease clinical and experimental studies leave no doubt that persons with beriberi are greatly benefited by vitamin B_1 therapy

It appears that man cannot synthesize vitamin B_1 nor can he store it to any great extent The length of time a deficiency must exist or the degree to which it must be present before clinical evidence of the disease

at least 4000 calories per day, the diet should include 1500 cc sweet milk ½ pound lean meat or liver, and eight eggs Additional milk should be given instead of water except in very dehydrated cases Water tends to decrease the amount of food ingested, the milk will not only supply fluid but will also be an additional source of nourishment Diets abnormally high in carbohydrate or fat content are contraindicated The diet should be supplemented especially at night by large amounts of a potent specific therapeutic agent prepared by a reputable concern When administered by mouth dry powdered brewers yeast (30 Gm three times daily) crude liver extract (30 Gm three times daily) wheat germ (60 Gm three times daily), or nicotinic acid or nicotinic acid amide (10 doses 50 mg each daily) are effective The amide is preferable to nicotinic acid when one wishes to avoid vasodilating reactions

Treatment of the Severe Case—The severe case that is one with central nervous system involvement intractable diarrhea persistent vomiting marked anemia a pulse rate exceeding 120 or a temperature of 103° F must have immediate supportive as well as antipellagric therapy As in the mild case success of treatment depends upon improved nutrition adequate rest and appropriate medical and nursing care The food intake must be increased to at least 4500 calories per day The specific therapeutic agent must be administered in amounts three times as large as those used for the mild case Absolute rest in bed is imperative Parenteral liver extract (probably the crude preparation is more efficacious than the refined) given intravenously or intramuscularly in doses of 20 cc three to five times daily in addition to the wheat germ yeast or liver extract by mouth is often beneficial especially to patients with persistent vomiting or diarrhea Nicotinic acid orally (50 mg ten times daily) or parenterally (25 mg in physiologic solution of NaCl two or three times daily) is astoundingly effective Healing of the oral and dermal lesions even in the most severe cases usually begins within seventy two hours after treatment is begun and the relief of the psychoses of pellagra is spectacular

Special Treatment of Symptoms—Symptomatic treatment often aids in remitting the disease Exacerbation of the stomatitis vomiting diarrhea and abdominal pain must not deter the physician from continuing the administration of proper diets specific therapeutic agents and indicated symptomatic therapy

Oral Lesions—The use of a mouth wash is beneficial The teeth should be brushed gently to avoid severe hemorrhages

Skin Lesions—Potassium permanganate solution (1 5000) used as soaks offers some relief and in the moist type of lesion diminishes the possibility of secondary infection

Diarrhea—Tinctura opii 2 cc., can be given every four hours unless symptoms of overdosage appear This is sometimes beneficial and is particularly indicated whenever an analgesic is required The severe case should receive fluids by a parenteral route The administration of nicotinic acid is effective

Vomiting—Absolute rest in bed and feedings of an iced fluid such as eggnog ginger ale or malted milk in small quantities (10-15 cc) at intervals of ten to fifteen minutes are necessary and should be continued until the patient has not vomited for twelve hours Either yeast wheat germ or liver extract should be added to these feedings in amounts of 4 to 5 Gm until the daily requirement has been given In the more severe case parenteral liver extract must be given immediately and continued until the patient is able to retain the required amount of the recommended diet together with any one of the potent specific therapeutic materials

Abdominal Pain—The pain often increases after meals thus discouraging the patient from eating Codeine will relieve this and should be used generously

Anemia—If the hemoglobin is below 50 per cent blood transfusions should be given After recovery has started large doses of iron should be administered

Fever—Alcohol sponges are indicated when the temperature is more than 103° F

Tachycardia—Patients with tachycardia must have constant rest

Mental Symptoms—Large doses of nicotinic acid result in spectacular relief of the mental symptoms and its use is indicated instead of sedatives

He is weak has a rapid, irregular pulse edema of the legs, and usually dies suddenly or is rapidly and completely cured by treatment

In contrast the onset in the adult is usually insidious and the prodromata are vague and general Lassitude general itching, dyspepsia tachycardia fatigue on exertion and tenderness of the muscles occur early After a variable period of time the symptoms can be associated with degeneration of the nervous system alteration of the gastro intestinal tract the presence of edema and serous effusions or enlargement and dilatation of the heart When the disease affects chiefly the peripheral nerves it is commonly called the dry type when it is especially characterized by acute cardiac symptoms it is known as the fulminating type and when it is associated primarily with edema and serous effusions it is referred to as the wet type Beriberi strikingly selects the vagi the peripheral nerves of the extremities and the vasomotor system

All symptoms are not necessarily present in a given patient and the order of their appearance may vary A patient with predominating cardiac symptoms may suddenly develop gastro-intestinal symptoms such as a distaste for food vomiting or diarrhea the patient with gastro intestinal distress may suddenly display such myocardial symptoms as dyspnea precordial pain and circulatory failure Either or both of the foregoing types may have or may develop peripheral neuritis and conversely a patient with peripheral neuritis may have cardiorespiratory or gastro intestinal symptoms Serous effusions and edema may precede accompany or follow the cardiac gastro intestinal or nervous symptoms

The symptoms subside slowly in the adults who recover many months may pass before there is a restoration of function if indeed complete restoration ever does take place Often after the active phase of the disease disappears residual paralysis muscular atrophy and cardiac enlargement remain for long periods of time

Nervous Symptoms —The chronic cases have involvement of the nervous system The early course is characterized by tingling of the hands and feet and by weakness of the legs The clinical manifestations are caused by an ascending symmetrical peripheral neuritis The deep reflexes of the extremities at first increase later diminish and finally are absent Tenderness in the calf muscles and sharply defined patches of anesthesia and numbness often appear early This process affects particularly the extremities and sometimes the diaphragm producing wasting of the muscles contractures ataxia lack of coordination and dyspnea Sensations of touch pain and temperature are usually decreased but at times they may be increased Anxiety states and mental confusion are common manifestations

Cardiorespiratory Symptoms —When the disease is characterized especially by cardiac symptoms (fulminating type) the adult patient usually dies suddenly and without a history of prodromal symptoms Occasionally however a person with gastro intestinal and neurologic symptoms suddenly develops the fulminating type of the disease The cardiac symptoms are always striking The most common ones are palpitation tachycardia dyspnea lowered blood pressure cardiac murmurs changes in the electrocardiogram and paralysis of the diaphragm Before death there is nearly always cardiac enlargement and dilatation pulmonary congestion edema cyanosis and vasomotor collapse

Digestive Symptoms —Frequently there is nausea vomiting and epigastric distress These symptoms are especially prominent in the acute fulminating type and are often found with cardiac decompensation

Other Symptoms —Edema is the most striking feature of many cases It usually begins in the legs and may progress until the whole body becomes involved Sometimes a typical case with the body bloated from anasarca appears emaciated following diuresis Polyuria is marked as the edema disappears but the amount of urine is decreased when the edema is increasing Hydropericardium and effusions into various serous cavities are common and a low serum protein can be demonstrated frequently At times the organs of taste smell hearing and sight are involved Libido decreases Anemia may appear in the later stages of the disease

Diagnosis —The typical case can be read

appears is not known Clinical studies show that the depletion period is extremely variable ranging from a few weeks to months or years They show also that certain factors predispose to and precipitate the development of the disease Prominent among these are increased physical exercise fevers hyperthyroidism and other conditions which are accompanied by an increased metabolic rate pregnancy and lactation digestive disturbances and chronic

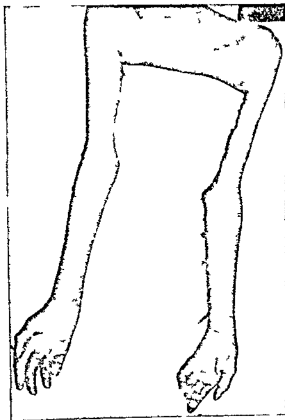


Fig. 51 —Muscular atrophy of the upper extremities in a beriberi patient with severe peripheral neuritis Compare the wasting of all muscle groups in the arms with fairly normal muscles of the shoulder girdle and neck

debilitating diseases which cause improper ingestion assimilation or utilization of food

At the present time the precise manner in which a deficiency of vitamin B_1 operates to produce the symptoms of beriberi is not understood It has been shown however that cocarboxylase (thiamin pyrophosphate) has antineuritic properties and that it is a fundamental enzyme which plays a prominent role in oxidation and reduction

There is considerable evidence that other nutritional diseases often coexist with beriberi Persons with beriberi frequently have a deficiency of nicotinic acid and riboflavin and symptoms which arise from these deficiencies are benefited by the administration of these synthetic chemical substances The number of factors involved in the development of the disease is not known and knowledge concerning the physiologic mechanism is incomplete Nevertheless the synthesis of vitamin B_1 (thiamin), nicotinic acid and riboflavin has stimulated investigation and during the next few years much of the confusion over the relationship between the various symptoms of beriberi and between beriberi and other diseases should be eliminated

Morbid Anatomy—Postmortem examinations are of little value in making a diagnosis or in explaining the pathologic physiology of the disease The findings are not constant but the process in general is one of degeneration affecting especially the myocardium the gastro intestinal tract and the nervous system The most common gross findings are emaciation of the body and atrophy of the muscles particularly in the legs The body is often edematous the heart is dilated and hypertrophied and serous effusions and chronic passive congestion of the viscera are commonly observed Microscopic studies show diffuse edema in various tissues and degeneration of the involved nerves muscles and myocardium Degeneration of the nerves varies from slight alteration to complete degeneration of the myelin and axis cylinder The affected muscles show a diffuse parenchymatous degeneration with loss of striations and hyaline and fatty changes The cardiac muscle fibers are often fragmented and contain hyaline and fatty material Postmortem findings in infants dying of beriberi are practically identical with those found in the adult The degenerative changes in the nerves are however less striking in the infant

Symptoms—Beriberi may be an acute or chronic disease In the infant it is nearly always acute in the adult it is nearly always chronic The symptoms of infantile beriberi appear identical with those of the fulminating type in the adult Infantile beriberi is characterized by a rapid onset with diminished urinary secretion constipation rigidity of the body and cyanosis The child has a peculiar whine and cries most of the time

for every case in which the diagnosis of beriberi is established It may be administered intravenously intramuscularly or orally Parenteral administration is recommended in severely ill cases especially when vitamin B_1 deficiency is associated with severe gastro enteric disturbances or with cardiac failure In such cases 30 to 50 mg should be given intravenously in sterile physiologic saline twice daily For the average case the parenteral administration of 10 mg twice daily is adequate Oral administration of 5 to 10 mg twice daily is sufficient for the mild case Brewers yeast wheat germ and tikitiki (an alcoholic extract of rice polishings) are effective therapeutic agents in the average case of vitamin B_1 deficiency The usual dose of brewers yeast and wheat germ is 6 ounces and of tikitiki 3 ounces The yeast and wheat germ are best tolerated if given in iced milk or egg nog at frequent intervals All persons who have a vitamin B_1 deficiency should be given a well balanced high caloric diet including foods rich in vitamin B_1 These foods are whole grain bread and cereals legumes lean pork liver heart kidney and milk All patients whether the disease is mild or severe should be kept at complete rest until convalescence is well established

For infants with beriberi the parenteral administration of from 5 to 10 mg of crystalline vitamin B_1 is recommended After convalescence is established the same amount may be administered orally If crystalline vitamin B_1 cannot be procured an alcoholic extract of 100 Gm of rice polishings (tikitiki) may be given daily If the child s mother has latent or manifest beriberi cow s milk should replace breast milk

Tom D Spies

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RIBOFLAVIN DEFICIENCY

The importance of riboflavin in human nutrition was observed independently by Sebrell and Butler and Vilter Vilter and Spies Riboflavin deficiency occurs in either sex at any age and is common in persons who subsist over a considerable period of time on a grossly inadequate diet It tends to occur in the spring and to disappear during the summer months

Diagnosis depends upon the recognition of characteristic angular stomatitis associated with transverse fissures in the corners of the mouth Another lesion occurring less frequently is the accumulation of greasy seborrheic material around the alae nasae and occasionally around the eyes and on the ears In the Nutrition Clinic of the Hillman Hospital Birmingham Alabama we have observed over 5000 persons with riboflavin deficiency In our experience we have found that diagnosis depends upon the recognition of certain symptoms and their response to the administration of synthetic riboflavin or substances containing riboflavin The symptoms characteristic of riboflavin deficiency are angular stomatitis associated with transverse fissures in the corners of the mouth and lips (Fig 52) and an abnormal shiny redness of the mucous membranes of the lips a sharkskin appearance of the skin around the alae nasae eyes and occasionally over the ears and malar prominences ocular symptoms characterized by bulbar conjunctivitis lacrimation burning of the eyes and failing vision and invasion of vessels of the cornea These symptoms disappear within four to six days following the

ily diagnosed by means of a reliable dietary history and by the presence of certain characteristic physical findings Almost without exception the history reveals that adults who develop beriberi have subsisted on a monotonous diet abundant in carbohydrates (chiefly milled rice wheat or corn) The physical findings are an enlarged heart peripheral neuritis edema and tenderness and atrophy of the muscles Infants who are restricted to the milk of women with beriberi usually develop the disease during the first three months of life The diagnosis is made on the following objective findings constipation diminution in the volume of urine rigidity of the body, irritability, a rapid and irregular pulse weakness edema cyanosis and a peculiar whine

While the atypical or mild cases occurring in infancy or later are probably more common than the typical ones the manifestations in such cases vary greatly and the disease is not easily recognized Since there is no specific laboratory test for beriberi it is often necessary to exclude the possibility of various types of heart disease diphtheria nephritis tabes alcoholism lead and arsenic poisoning pellagra scurvy and sprue before a positive diagnosis of beriberi can be made

Prognosis—No disease requires more conservatism in making a favorable prognosis than does beriberi for a patient who seems to be recovering may suddenly develop cardiac symptoms and die The mortality rate is variable being around 5 per cent in the mild cases and reaching well over 50 per cent in the more severe ones The ultimate prognosis is dependent upon the age and general condition of the patient and upon the severity and duration of the disease In general patients with acute cardiac symptoms are least likely to survive If the adult is left untreated eventually incapacitation or even death is to be expected If however the disease is recognized and treated early the outlook is good provided the patient can and will follow recommendations Recovery is rapid and complete in infants who are given early and persistent treatment

Prevention—Prevention in the adult or infant is dependent upon the ingestion assimilation and utilization of sufficient quantities of a well balanced diet Beriberi would practically disappear if it were possible to make proper diets available to all We cannot hope however to achieve this ideal in the immediate future as its fulfilment is dependent upon educating the masses and raising their economic level The most logical means of ending beriberi as a world problem in the near future would be to pass and enforce a law preventing the overmilling of rice wheat and corn Grain products have long been the principal component of the poor man s diet Overmilling of the cereals has deprived the finished product of much of its natural mineral and vitamin content Consequently the foods which may constitute the major part of the diet of persons most in need of improvement in their nutritional status are nutritionally inferior The enrichment of flour and bread in this country is a step forward in improving the diets of these persons Until such time as proper diets are available to all people or until a law prohibiting the sale of overmilled cereals is passed and enforced the incidence of beriberi can be greatly decreased by the application of the following recommendations

1 Whole grain or enriched flour and bread should be substituted for the highly milled products

2 Foods must not be overcooked as excessive heat destroys vitamin B_1 The common habit of adding soda during the cooking process is detrimental and should be discontinued Foods should be cooked in as little water as possible and the water in which they are cooked should be used in soups or broths rather than discarded

3 Lean meat milk eggs fresh vegetables dried vegetables and nuts should make up at least 50 per cent of the daily diet

4 Any one of the following relatively inexpensive supplements is helpful in preventing beriberi and should be added to the daily diet whenever possible dried brewers yeast (1 ounce) wheat germ (2 ounces) or tikitiki (1 ounce) Infants are given indirect protection by preventing the disease in mothers and can be given additional protection by supplementing their daily diet with an alcoholic extract of 40 Gm of rice polishings (tikitiki)

Treatment—Crystalline vitamin B_1 (thiamin hydrochloride) is recommended

10 mg of thiamine 50 mg of niacin, 5 mg of riboflavin and 75 mg of ascorbic acid When we find that the symptoms of one deficiency disease predominate we add to this formula more of the vitamin specific for the predominating deficiency In the case of beriberi 10 mg of thiamine are added daily in riboflavin deficiency, 5 mg of riboflavin twice daily in scurvy 100 mg of ascorbic acid three times a day and in mild pellagra 50 mg of niacin amide three times a day If the pellagra is severe the patient is given 150 mg of niacin amide three times a day in addition to the basic formula When the patient is moribund it may be necessary to resort to parenteral injections in order to prolong and indeed even to save life When large amounts of *d* glucose are injected daily we recommend the inclusion of 20 mg of niacin amide 7.5 mg of riboflavin and 5 mg of thiamine In a few instances we have found it desirable to inject 50 mg of ascorbic acid in physiologic solution of sodium chloride

Dried brewers yeast powder liver extract wheat germ and rice polishings are excellent therapeutic agents for the treatment of diseases arising from a deficiency of the B complex vitamins These substances are particularly valuable in that they contain significant amounts of protein and other essential nutrients and probably vitamins of the B complex as yet unknown The amount administered depends upon the severity of the disease We usually give daily from 120 to 180 Gm of dried brewers yeast powder or oral liver extract from three to four doses of 20 cc of parenteral extract or from 150 to 300 Gm of wheat germ For prevention or supplementary treatment smaller doses are used

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Symposium on Nutrition T D Spies Ed Med Clin North America, 27 March 1943

SPRUE

Definition —Sprue is a chronic afebrile disease with a marked tendency to remissions and relapses When *fully developed* it is characterized by glossitis gastro intestinal indigestion meteorism diarrhea with the passage of voluminous fatty frothy foul smelling stools great loss of weight generalized muscular wasting with asthenia and (in adults) by a macrocytic hyperchromic anemia

History —The earliest clearly recognizable description of the sprue syndrome was given by Aretaeus the Cappadocian in the second century A D Sprue is the English form of the Dutch word 'Sprouw meaning aphthous stomatitis The term was first used by Vincent Katelaer in 1669 in describing a disease among the Belgians characterized by aphthous stomatitis and by fecal discharges so copious "that several basins or pots scarcely hold these accumulations" William Hillary's description of sprue as observed in the Barbados was first published in 1759 The modern conception of sprue however dates from the publications of Manson and of Van der Burg in the same year 1880 Samuel Gee in 1888 gave a brief but classic description of a wasting disease of early childhood associated with copious fatty stools, which he called "the coeliac disease" He indicated however that it might occur in patients of any age

Incidence —The disease has long been known as tropical sprue because of its endemicity in certain tropical regions For North American physicians however it is important to emphasize that the sprue syndrome occurs in the United States *both north and south and that it is often wrongly diagnosed* Recent investigations indicate that tropical sprue' nontropical sprue and 'celiac disease are manifestations of the same morbid condition

Etiology —The exact etiology is unknown but the generally accepted view today is that the sprue syndrome is the result of nutritional deficiency and the remarkably beneficial action of liver in the treatment of the disease strongly supports this conclusion It is possible that the deficiency in sprue may arise in four ways (1) by a dietary deficiency of the extrinsic factor (to use the terminology of Castle) (2) by a defect of gastric digestion due to lack of the intrinsic factor (3) by poor absorption from the intestine and (4) by deficient storage by the liver A combination of several of these defects may exist Recurrent attacks of sprue often are associated with pregnancy

By feeding to swine a diet deficient in certain food factors Rhoads and Miller have produced a disease which very closely simulates sprue Ashford ascribed the onset of

administration of adequate amounts of riboflavin

Treatment —In the average case, the administration of 5 mg of synthetic riboflavin t i d was followed by the disappearance of the lesions within three to six days Each of two patients who were given 2 mg of synthetic phosphoric acid ester of riboflavin t i d showed similar improvement within six to eight days In the above cases Ashe and Spies found that the daily excretion of flavin (determined as riboflavin) was 18 per cent below normal Diminished output of

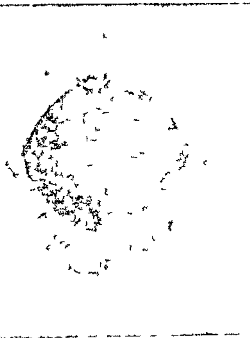


Fig 52 —Cheilosis (angular stomatitis) a characteristic lesion of riboflavin deficiency appeared in this young woman following cyclic vomiting

flavin has been observed in other patients who have not had the typical lesions described above Following the administration of riboflavin the level in the urine rises These studies suggest that in persons subsisting on inadequate diets riboflavin deficiency is not uncommon Our figures indicate that the riboflavin requirement for an adult is approximately 3.5 mg daily

Comprehensive reviews of the physiology and pathology of riboflavin deficiency and on the chemical nature of riboflavin have been published and its importance in human nutrition has been established but at the present time the exact mechanism of its action is not understood Nevertheless it is known that the lesions of riboflavin deficiency disappear and the patient has an increased feeling of well being following the ingestion of an adequate well balanced diet the administration of brewers yeast or synthetic riboflavin

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MIXED DEFICIENCY DISEASES

Diets that fail to supply one nutrient in adequate amounts are deficient in others and every method of study has indicated the predominance of mixed rather than single deficiencies Accordingly a person may develop a number of diseases simultaneously although diagnostic evidence of only one may be apparent at the time he is examined by the physician The basis of treatment of all patients with deficiency diseases is a diet that supplies liberal amounts of all the essential nutrients In many instances however food cannot be consumed in sufficiently large amounts to supply the patient with the quantities of nutrients needed to restore him to health Too often it is forgotten that we must treat the patient rather than hi disease and that treatment must be adapted to the individual case Even a liberal well balanced diet should be supplemented with all the vitamins known to be essential for human nutrition They may be given as crystalline vitamins as concentrates or in the form of therapeutic materials such as dried brewers yeast or liver extract

In treating the clinical syndromes of beriberi pellagra riboflavin deficiency and scurvy we give a basic formula consisting of

in sprue from two to three times the normal amount is found Frequently it can be demonstrated microscopically by staining with Sudan III but only exact quantitative analysis can be depended upon to reveal the excess of fat Although the total fat of the stool is greatly increased, the end products of fat digestion are not relatively altered from the normal indicating normal lipolysis The pancreatic enzymes are present in normal amounts in the duodenal contents The difficulty would seem to be one of assimilation rather than of digestion and several observers have shown that there is a low blood fat curve after feeding fats similar to the low blood sugar curve after the ingestion of glucose The loss of nitrogen is slight and sprue patients digest and absorb proteins readily An excess of calcium may be excreted in the stools producing low serum calcium values Serum phosphorus is also low but in this case the excessive excretion is by way of the urine

Blood Sugar Curve—Thaysen first observed that in patients with sprue following the ingestion of 1.5 Gm of glucose per kilo of body weight a low blood sugar curve was a frequent finding whereas less than 5 per cent of normal individuals show this type of curve The test is very valuable and deserves the widest application It offers an easy and reliable aid in the differentiation of sprue from pernicious anemia pancreatogenous steatorrhea and tabes mesenterica diseases with which it is most liable to be confused In 54 sprue patients observed at Duke Hospital none of whom had been in tropical countries and only one of whom had even lived outside the state of North Carolina the maximum rise in the blood sugar curve following the ingestion of 1.5 Gm glucose per kilo of body weight was 39 mg per cent the minimum 4 mg per cent and the average 20 mg per cent In ten pernicious anemia patients similarly tested none showed a rise of less than 40 mg per cent and the average rise was 59 mg per cent In pancreatogenous steatorrhea the blood sugar curve is diabetic in type Glucose given *intravenously* (0 2 Gm per kilo of body weight) produces a normal response in the blood sugar curve

Blood—In early sprue a mild hypochromic anemia may be found but this soon changes to a macrocytic hyperchromic anemia which cannot be distinguished from the blood picture of pernicious anemia Bone marrow, obtained by sternal puncture, is

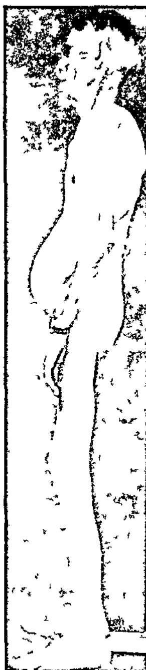


Fig 53—Sprue cachexia

indistinguishable from the hyperplastic megalocytic marrow of pernicious anemia As the patient improves the blood becomes either normal or hypochromic In infantile

the disease to the preponderance in the diet of carbohydrate and fatty foods and a deficiency in proteins, a view which has been widely adopted He thought however that this nutritional imbalance led to gastro intestinal conditions favorable to the growth of a yeastlike fungus *Monilia psilosis* which in turn aided in producing the clinical picture known as sprue The studies of Castle and Rhoads on sprue in Puerto Rico do not substantiate Ashford s theory of the pathogenic action of *Monilia* and there is no acceptable evidence that sprue is an infectious disease

Morbid Anatomy —There are no pathologic changes characteristic of sprue The gastro intestinal tract frequently shows marked atrophy of the mucosa and thinning of the walls The colon is often greatly dilated The parenchymatous organs especially the liver and spleen are smaller than normal and the storehouses of fat are remarkably depleted The disease literally dissects the patient

Symptoms —All the symptoms of sprue are due to dysfunction of the gastro intestinal tract In the beginning the patient suffers from recurring attacks of indigestion with flatulence and diarrhea of varying severity alternating with constipation The tongue and mouth may or may not be sore In early or mild cases the episodes of diarrhea may be so slight that only questioning brings them to light The sprue patient may pass but one large fluid foul smelling stool daily A carefully taken nutritional history may reveal that the patient has subsisted upon a badly balanced diet composed of an excess of carbohydrates and fried foods and a deficient amount of meats Not infrequently the indigestion and diarrhea have caused a further limitation of protein intake Defective teeth and poor oral hygiene are common causes of a poor or perverted appetite and idiosyncrasies of diet once established often are fixed by habit However no history of dietary peculiarities can be obtained in some sprue patients Gradually the sense of well being is lost and the patient feels generally miserable Such patients are very commonly diagnosed as neurasthenic and their gastro intestinal symptoms explained as due to a neurosis

If the nutritional deficiency is unrecognized and untreated the complete picture of sprue gradually develops with exacerbations and remissions characterizing its course The patient is now no longer ailing but actually ill The entire gastro intestinal tract shows evidence of disease the tongue and mouth often become sensitive to hot or seasoned foods and crops of small very sensitive aphthous ulcers may appear on the buccal mucous membranes Epigastric distress vomiting and intestinal colic are complained of and the stools become more frequent, bulky light in color frothy and foul smelling The diarrhea is especially troublesome in the early morning several voluminous stools being passed before breakfast The appetite fails and the patient emaciates rapidly It is not uncommon for one third or one half of the normal weight to be lost in striking contrast to pernicious anemia in which the loss of weight usually is moderate

In fully developed sprue the patient often presents the picture of an asthenic mentally depressed unhappy individual with almost complete anorexia The skin is rusty grapefruit colored and occasionally symmetrically pigmented the panniculus adiposus gone, the abdomen protuberant and the bones show through as though the patient were a living skeleton The tongue is beefy red and sore showing marked papillary atrophy Paresthesia of the hands and feet is quite common and in rare instances subacute combined degeneration of the spinal cord has been observed

Diagnosis —Sprue may occur at any age The infantile form which begins as a rule in the second year is known as celiac disease or chronic intestinal indigestion and owing to generalized malnutrition with deficiency of calcium and phosphorus dwarfism rickets and tetany are not infrequent features of the clinical picture Osteoporosis and tetany are seen in adult sprue Older patients who have suffered from sprue in infancy or early childhood frequently show dwarfism with or without marked bony deformities The blood proteins may fall low enough to cause a moderate edema

Stools —Steatorrhea is characteristic of sprue but not pathognomonic of this disease In the normal stool not more than 15 per cent of the dry weight is fat whereas

has become irreversible and even maximum therapy will yield poor results The liver therapy must be *adequate* to control the symptoms regardless of the amount and the parenteral route is the method of choice Liver therapy must be more intensive in sprue than in pernicious anemia for although the blood responds readily to treatment the gastro intestinal tract is much slower in returning to normal In long standing cases of sprue especially in the aged the tendency to recurrence of steatorrhea may persist for years Such patients will require maintenance doses of liver to control the diarrhea even when the blood has been restored to normal

Since sprue patients assimilate fats poorly these should be restricted at first to 25 or 50 Gm daily and only gradually increased with cessation of diarrhea In some patients because of meteorism carbohydrates must be reduced Ripe bananas and banana flour are well tolerated Under the influence of adequate liver therapy the glossitis quickly heals the papillae regenerating with astonishing rapidity and the appetite improves so promptly and remarkably that the feeding of a full generous diet usually is possible at once A high protein high vitamin diet is recommended and this alone may control the early or mild cases Brewers yeast or autolyzed yeast (vegex marmite) 1 teaspoonful in a glass of warm water after each meal has proved useful but may cause distressing meteorism

As the blood count rises the color index falls and iron should be given early in full doses Calcium lactate and phosphate (of each 2 Gm 30 grains) should be given daily and if evidence of deficient calcification is present vitamin D (viosterol, percomorph oil) should be added

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sprue macrocytic hyperchromic anemia is very rare though it does occur The bone marrow in childhood seldom reacts to injuries in a macrocytic hyperchromic manner, and therefore pernicious anemia is very rare in children

Gastric Analysis —Achlorhydria after histamine stimulation (0.5 mg) does not occur in sprue more frequently than in normal individuals Hypochlorhydria is the rule but as the patient improves under proper treatment the free HCl increases and if it has been absent it may return Of 50 cases of sprue observed in Duke Hospital by the writer 21 per cent showed an absence of free HCl in the gastric juice after histamine stimulation Ogilvie found that two of fifteen patients (13 per cent) with celiac disease had achlorhydria after histamine stimulation

The differential diagnosis of sprue in its earlier stages may be difficult If however the clinical features of the disease are borne in mind a careful history elicited with especial reference to nutritional deficiencies and if the blood stools and blood sugar curve are thoroughly studied evidence pointing to the deficiency state called sprue will be uncovered *Great loss of weight steatorrhea a low blood sugar curve and megalocytic hyperchromic anemia are four findings characteristic of sprue*

Pernicious anemia frequently has been confused with sprue because of the glossitis and macrocytic hyperchromic anemia common to both These are really their only essential points of resemblance Achlorhydria after histamine stimulation is a constant finding in pernicious anemia the blood sugar curve is not low, diarrhea may occur but is not fatty and the progressive emaciation so characteristic of sprue is not a part of the clinical picture of pernicious anemia The two syndromes present more differences than similarities and by using modern methods of study there should be no excuse for confusing them It is not improbable that the reported cases of pernicious anemia with free HCl in the gastric juice were in reality instances of the sprue syndrome The differentiation of pernicious anemia from sprue is of the utmost importance for in pernicious anemia the patient is condemned to a lifetime of troublesome and expensive therapy whereas in the light of present knowledge it is believed that sprue is as a rule curable provided that the underlying dietary deficiency is permanently corrected

Pellagra and Addison s disease bear only a superficial resemblance to sprue and should cause no real diagnostic difficulties Pancreatogenous steatorrhea unlike the diarrhea of sprue is characterized by great loss of nitrogen in the feces (azotorrhea) which can be demonstrated microscopically in the form of undigested striated muscle fibers, and the blood sugar curve is diabetic in type

Tabes mesenterica may cause steatorrhea, but the blood sugar curve is not low the anemia is hypochromic and the finding of tuberculosis elsewhere in the body clarifies the diagnosis

Steatorrhea and azotorrhea may follow fistulous connections between the stomach and intestines and for understandable reasons an addisonian like anemia may thus be produced Such cases studied with the aid of x rays will not offer any serious difficulties in diagnosis

Prognosis —Sprue unlike pernicious anemia is a curable disease in the large majority of sufferers but if treatment is too long delayed unsatisfactory results and even failures may occur There would seem to be a stage in the natural history of the disease from which complete recovery is impossible with our present therapy On the other hand even the most advanced cases often respond in a satisfactory manner

Treatment —Until recently sprue was treated with a great variety of special diets which are now of only historic interest In 1927 Bloomfield and Wyckoff applied to a case of sprue with macrocytic hyperchromic anemia the liver treatment which Minot and Murphy had just shown to be efficacious in pernicious anemia They observed prompt improvement featured by rapid cessation of diarrhea a remarkable gain in weight and improvement of strength and well being The reticulocytes increased the blood count rose and finally a normal blood picture was established This has been the experience of many subsequent observers When treatment is begun early the response is brilliant but in a certain number of far advanced and long neglected patients the disease process

must be included in protective diets' like those of McCollum to prevent wastage of stored body protein The deposit" protein in the body as shown by Boothby constitutes a large reserve but varies considerably in extent with thyroid activity and is depleted in protein deficiency When adequate caloric intake is assured the minimal daily requirement of protein may be as low as 0 6 Gm per kilo but ordinarily one hopes for twice this amount including a goodly assortment of amino acids For growth and pregnancy a greater factor of safety is needed else large amounts of body protein may be destroyed to procure enough of a single amino acid The injection of peptone may produce 'pep tone shock in which extensive lysis of pro tein occurs In hyperthyroidism or fever increased assimilation of fat and carbo hydrate may spare protein but it is unde cided how infectious toxins act *per se*

When the intake of unsaturated fatty acids is too low Burr and Burr found that disease results Likewise when carbohydrate contributes less than 10 per cent of the total caloric intake increased azoturia and keto nuria occur in many individuals

oxidized normally A similar explanation may be given for cystinuria and pentosuria

In other instances the destruction of a particular organ may be the cause, as in the accumulation of amino acids in hepatic atrophy Less well understood is the accumu lation of liver glycogen in von Gierke s dis ease

Homeostatic Equilibria in Clinical Chemistry—The constancy of the *milieu interne* emphasized by Claude Bernard was studied by L J Henderson in physicochemi cal terms The acidity of the body fluids is maintained nearly constant locally by buffer systems Despite the acidic trend of human catabolism the kidney preserves neutrality by excreting acid phosphate for basic phos phate and by substituting ammonia for sodium With the rise of systematic clinical chemistry under the schools of Folin and D D van Slyke many other steady states have been disclosed Thus electrolyte patterns of the plasma in health and disease have been compiled by Gamble expressed in milli equivalents per liter so that ions of various atomic weights may be summated in com mon units A typical normal distribution is

Total base = total acid

Sum of cations (positively charged ions) = sum of anions (negatively charged ions)

Na	+ K	+ 2 Ca^{++}	+ 2 Mg^{++}	= Cl	+ HCO	+ f × protein	+ H_2PO	+ R †	
Expressed as milliequiv per liter									
142	+ 5	+ 5	+ 2	= 105	+ 25	+ 17	+ 2	+ 5	= 154
Expressed as vols per cent					48				
Expressed as mg per 100 cc									
327	+ 19	+ 10	+ 2 4	3,4		f × 7000	+ 3 1		

The net capacity of the combined plasma proteins to bind base at *p*H 7 4 is calculated by multiplying the factor *f* times the protein concentration

† Organic acid radicles plus sulfate

Intermediary Metabolism—In certain metabolic diseases the normal fate of a met abolite is blocked by failure of some cellular mechanism Thus Garrod in 1848 recog nized that in podagra uric acid accumulated in body fluids Likewise the acetone bodies of diabetic coma are natural intermediates whose normal pathway has become con gested because of excessively rapid fat cat abolism In thiamine deficiency pyruvic acid accumulates because natural mechanisms concerned with oxidation have failed In the xanthomatoses the reticulo endothelial sys tem is overloaded with lipoid the normal disposition of which has failed In the mental defectiveness studied by Folling phenyl pyruvic acid is excreted instead of being

When calcium rises phosphate tends to fall and vice versa Likewise in Addison s hypoadrenocorticism a fall in sodium usu ally is accompanied by a rise in potassium The total osmotic pressure can vary only within narrow limits and the sum of the cations must equal approximately the sum of the anions with due regard to the protein present Because the total base varies but little changes in the chloride and bicarbo nate ions tend to be reciprocal The intra cellular tissue fluids constitute a reservoir of body water and electrolyte from which losses from blood or cells may be replaced as shown by Peters

Most steady states depend upon some regulating action of the central nervous

DISEASES OF METABOLISM

INTRODUCTION

Energy Requirements in Health and Disease—Lavoisier measured the oxygen consumption of resting man and demonstrated that higher values were found during digestion during exercise and exposure to cold Subsequently Pettenkofer and Carl Voit applied the heats of combustion of the three principal foodstuffs to indirect calorimetry applicable to patients They found that the amount of oxygen required for metabolism depends upon the composition of the mixed foodstuffs being burned as judged by the respiratory quotient Voit showed also that the intensity of the caloric turnover regulated the amount of oxygen assimilated, but that even hard exercise did not increase protein catabolism Much later Atwater and Rosa with their large calorimeter demonstrated with nicety that the first law of thermodynamics applies to man

Rubner's finding that the caloric equivalent of the resting individual's metabolism is proportional to his surface area led to the formulation of standard tables for men and women by Harris and Benedict and by Aub and Dubois Plummer and Boothby introduced the term basal metabolic rate (B M R) to indicate in terms of surface area the relative intensity of bodily combustion at rest and in the relaxed fasting state The normal value is relatively high for infants rises again at puberty and declines gradually with advancing years Women show lower values than men but the basal caloric requirement for normal adults is approximately 25 calories per kilogram daily or 40 calories per square meter per hour Fever increases this value on the average by 7.2 per cent for each Fahrenheit degree of elevation It falls with inanition myxedema and lipoid nephrosis and rises with leukemia and hyperthyroidism

Obviously exercise increases the total daily caloric consumption far above the basal level so that a tailor might require only 2300 calories daily a carpenter 3300 and a lumberman 5000 It should be noted that medical usage has corrupted the kilogram calorie or Calorie to "calorie"

The Fundamental Foodstuffs—By 1840 Liebig had accepted the principle of nitrogen equilibrium in health and the concept of a maintenance ration On multiplying fecal and urinary nitrogen excretions by 6.25 protein metabolism could be estimated approximately and the nonprotein respiratory quotient used to measure the proportion of fat and carbohydrate being burned When carbohydrate is burned the volume of carbon dioxide produced per volume of oxygen consumed gives a ratio of 1 0, whereas the respiratory quotients for average protein and average fat are 0 78 and 0 71, respectively In fasting the R Q may fall to 0 69

Rubner's standard values for the energy values of the primary foodstuffs in kilogram calories per gram were 4 1 for protein 4 1 for carbohydrates, and 9.3 for fat The latter two values have been verified by combustion in the calorimetric bomb but one fourth of the energy of combustion of meat protein is lost to the animal Rubner also found that the specific dynamic action of ingested foodstuffs maximal after three hours, was 30 per cent for protein 6 per cent for carbohydrate and 4 per cent for fat The actual cause of this dietary increase in resting metabolism remains unknown Rubner's 'iso dynamic' principle stated that within certain limits 100 grams of fat could be removed from a balanced diet and replaced by 232 Gm starch 234 Gm cane sugar or 243 Gm dried meat Of course this principle is limited by certain other requisites a minimal demand for essential amino acids a minimal need for carbohydrate to spare protein and to prevent an undue demand upon fatty acid catabolism, and adequate supplies of accessory foodstuffs such as vitamins and minerals

By 1915 Osborne and Mendel had demonstrated the requirement of certain definite amino acids as building stones for body structure These include tryptophane histidine cystine and lysine (for growth), which

tends to mobilize these reserves Thus the effects of various hormones are mutually poised against the others The anterior pituitary provides a super-regulation through its several tropic hormones each specific for a peripheral endocrine organ When the thyroid or gonad is removed there is an increase in the circulating specific tropic hormone—the so-called "castration effect

By such reciprocal interplay of the pituitary thyroid axis" a steady rate of tissue combustion is achieved So nice is this balance that the microdetermination of protein bound iodine in the plasma may be used to measure net thyroid activity Thus in myxedema the value may be nearly nil in euthyroidism 5 to 7 micrograms per cent and in "thyroid storm 18 micrograms per cent

Measurement of plasma enzymes is occasionally useful The alkaline phosphate was utilized by Kay to study bone disease especially in disturbances of parathyroid function The acid phosphatase of the Gutmans reflects metastasizing prostatic cancer In acute pancreatic necrosis a sharp rise in serum amylase occurs

The concentration of hormones and enzymes in body fluids is much lower than that of metabolites like sugar or urea The former are expressed in *micro*grams per cent whereas the latter are stated in *milli*grams per cent. This thousand fold difference in concentration reflects the distinction between catalyst and substrate

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GOUT AND GOUTY ARTHRITIS

Definition —Gout is a disease of unknown origin characterized chiefly by (1) acute paroxysmal arthritis which is followed by complete remissions but which tends to recur later the arthritis may become chronic (2) a supposed abnormality in the renal excretion of uric acid the end product of purine metabolism this disturbance is also somewhat cyclic and varies in intensity (3) hyperuricemia, usually transient at first, later chronic (4) deposits of sodium urate crystals in articular periarticular and subcutaneous tissues sometimes also in kidneys these deposits generally appear in the later less commonly in the earlier phases of the disease (5) frequent terminal lesions in kidneys sometimes also in the vascular system of heart and brain

Etiology —Certain older hypotheses have been discarded or remain unproved. These were that gout resulted from (1) primary renal insufficiency causing retention and deposition of urates with resulting acute inflammation (2) disturbed blood alkalinity causing precipitation of urates (3) disturbance of the central nervous system (4) some hepatic dysfunction or (5) infection producing secondary metabolic abnormalities

Gout is commonly defined as a disturbance of purine metabolism The accompanying hyperuricemia has been considered the result of (1) excess formation (2) deficient excretion or (3) diminished destruction of urates in the body The idea of overproduction of urates seems untenable since no increased excretion or accumulation of phosphates accompanies the hyperuricemia as would be expected if destruction of nuclear protein were increased Investigators frequently have noted subnormal amounts of urates in the urine of gouty persons but this is not consistent or persistent Indeed some gouty patients both during and between acute attacks excrete more urates than nongouty controls (Talbott and Coombs) It has been suggested that gouty

system, but many such equilibria are largely kinetic rather than thermodynamic This "wisdom of the body" (Cannon) is frequently mediated through hormones It may be masked temporarily by digestion and absorption of food or by severe exertion or disease Tolerance tests are applied to try the inherent stability of such mechanisms under known strain Sometimes a deviation from the natural equilibrium serves a useful purpose Thus with the loss of electrolyte in high intestinal obstruction accumulating urea tends to compensate osmotically for loss of inorganic constituents

The existence of "renal thresholds" for glucose, calcium chloride and phosphate also serves to maintain homeostasis Thus a fall in serum chloride to 100 mEq/L or of calcium to 5 mg per cent, causes these substances to disappear from the urine Conversely at about 170 mg per cent glucose is excreted

The existence of these equilibria forms the chief basis for modern clinical blood chemistry Peters and Van Slyke have discussed them in detail The most useful procedure is to study equilibrium after overnight fasting but time curves following the administration of known material may be used to test metabolic tolerance The three principal classes of foodstuff are frequently examined in this way

Thus normal values for plasma protein usually range from 6.5 to 7.5 Gm per cent whereas for incipient edema the critical average values are 5 0 to 5.5 for total protein and 2.5 for albumin The blood urea nitrogen or the plasma nonprotein nitrogen reflects both the course of protein metabolism and the renal efficiency in clearing the organism of such waste products For the former normal values are usually between 9 and 14 mg per cent for the latter between 25 and 35 mg per cent Obviously low values may be found in inanition and after diuresis High values occur in dehydration heart failure and nephritis when excretion is poor or when protein breakdown is excessive as after severe burns Under special circumstances specific nitrogenous catabolites may be examined Thus the serum uric acid lies between 3 0 and 5 0 mg per cent and repeated fasting values above 6 0 suggest gout The blood creatinine normally ranging from 1 0 to 1.8 mg per cent, becomes elevated when renal clearance is poor Accordingly, in nephritis the prognosis is poor at 10 mg per cent and exitus is imminent at 18 mg per cent

Carbohydrate metabolism is reflected by the plasma glucose concentration normally about 70 to 100 mg per cent Many factors influence its magnitude particularly endocrine balance Likewise low values may occur in exhaustion or hepatic necrosis because liver glycogen reserves are low High values usually indicate sympathetic activity in the absence of diabetes mellitus Albright has used the glucose-insulin tolerance test to gauge the reserve of various endocrines especially the adrenal cortex, as an aid to diagnosis

Of the circulating lipoids blood cholesterol has been used most extensively In many laboratories normal values range from 140 to 170 mg per cent In hyperthyroidism the level tends to be low High values are found in pregnancy myxedema and in the "nephrotic syndrome" In liver disease also high readings may occur

The Regulators of Metabolism—Health is maintained by certain catalysts which are called hormones vitamins and enzymes Probably the hormones circulate about the body to regulate appropriate enzyme systems in individual cells Thus a single hormone may produce opposite effects in different tissues The vitamins may constitute specific key groups in such enzyme systems The central nervous system too is involved in neurohumoral mechanisms which control vital equilibria Thus C N H Long has demonstrated that diencephalic lesions cause excessive food intake with resulting formation of fat and so lead to obesity Likewise the neurohumoral action of sympathetic and parasympathetic nerves results in the liberation of sympathin E or I or of acetylcholine

Some hormones exert anabolic effects, others catabolic For example the adrenal medulla liberates epinephrine which causes the rapid liberation of energy stores Testosterone on the contrary favors the storage of protein thus increasing muscular development and growth of body hair Insulin exerts a conservative action which replaces stores of protein and glycogen despite the antagonism of the thyroid hormone which

even bony ankylosis sometimes ensues (Ludwig Bennett and Bauer)

Urates may be deposited as white dots or streaks in renal substance or as orange-colored gravel or calculi in renal calices Foreign body reactions occur about the interstitial urate deposits these with the lesions of arteriolar nephrosclerosis and some glomerular fibrosis constitute the tissue reactions of gouty nephritis

Pathogenesis —In considering the pathogenesis of gout one must separate it into its components and study their interrelationships The agent or agents which cause the gouty state the acute gouty arthritis and the vascular complications are unknown Urate deposits may well be the chief cause of gouty nephritis and of chronic gouty arthritis When articular tissues can no longer cope with the reactions to urates chronic gouty arthritis develops Disturbances of uric acid are now considered the result not the cause of the disease Recent studies indicate that in gout cyclic variations in the excretion of several salts besides urates occur (Talbott Jacobson and Oberg) Hyperuricemia or urate deposits likewise are not considered the cause of acute attacks because marked hyperuricemia accompanies other diseases (*e g* leukemia) without commonly invoking gouty arthritis There is no consistent relationship between acute attacks and formation of tophi or the degree of hyperuricemia acute attacks are relieved by colchicine which has no known effect on the urinary or on the total blood uric acid (But it may lower the bound uric acid in serum)

Symptoms.—*Classic Gout.*—The chief features of gout (the arthritis hyperuricemia tophi and late renal and cardiovascular complications) are only the outward signs of some fundamental chemical or metabolic disturbance of which little is known This disturbance called 'gout per se' or gouty diathesis is probably symptomless for some time before acute arthritis first appears and under suitable provocation causes the subsequent appearance of the classic symptoms During the larval stage of gout the body is being unobtrusively conditioned for subsequent events but what chemical or histologic abnormalities are then transpiring is unknown

Evolution of the Continuing Pattern of Gouty Arthritis —Gout and gouty arthritis are not synonymous the latter is merely the dominant symptom of gout Gout can best be studied by noting the relationship of its other features to the pattern of gouty arthritis (Fig 54) The first attack of acute gouty arthritis usually occurs suddenly lasts about three to ten days and then disappears completely It affects a great toe or with almost equal frequency an instep ankle knee or other region The typical acute attack often comes on at night The pain which is at first moderate increases in intensity In severe attacks the pain is so intense that even the weight of the bed clothes and the vibration of the bed add to the patient s distress Toward morning the pain abates and the patient may fall asleep On examination the affected joint is swollen and exquisitely tender The skin is of a deep red color sometimes almost purplish and

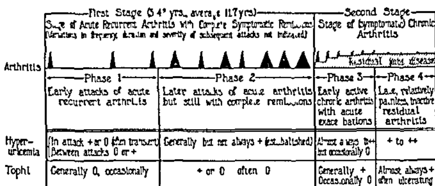


Fig 54 —The basic pattern of gout and gouty arthritis (untreated) (Hench P S J Lab and Clin Med Oct., 1936)

patients are deficient in some purinolytic ferment, hence do not destroy urates adequately, but others insist that man does not possess the property of uricolysis, still others have believed that gouty patients destroy unusual amounts of urates, hence excrete subnormal amounts Whether or not gout is to be considered a disturbance of purine metabolism depends on the definition of such disturbance Gouty persons apparently catabolize foods through the same successive steps from purine bodies to uric acid as do normal persons, hence there is no obvious abnormality of intermediary purine metabolism Thus gout is not truly a disturbance of purine metabolism even though it involves a faulty disposition of urates

Newer opinions are that gout results from (1) some endocrine deficiency, (2) abnormal renal insensitivity to urates (3) selective renal insufficiency for urates alone (4) a "storm in the vegetative nervous system" a functional disturbance involving thoracic (Tinck) or renal (Grabfield) sympathetics or (5) an allergic reaction to proteins not necessarily to exogenous proteins derived from foods rich in purine, but also to proteins from nonpurine foods as well as to endogenous proteins tissue substances formed after injuries vasomotor disturbances or surgical operations

Incidence of Factors Governing Gout—Contrary to the belief of many physicians gout has not disappeared it is seen with increasing frequency by those looking for it At the Mayo Clinic patients with classic gout constitute at least 5 per cent of those seen by consultants on diseases of joints Reported statistics on the incidence of gout often give an inaccurate idea of the situation because the diagnostic criteria of various physicians differ materially Gout is recognized in private practice much oftener than in general hospitals

Several predisposing factors govern the incidence of the disease

Sex—Classic gout may affect females but about 95 per cent of patients are males If a writer states that many more than 5 per cent of his gouty patients are females his diagnostic criteria are open to question An interesting case of gout and male hermaphrodism has been reported recently (Rosenberg)

Age—Symptoms first appear generally among persons aged thirty five years or more occasionally among persons aged sixty or seventy years and rarely among children in their teens When juvenile gout occurs the hereditary factor is more apparent and the progress of the disease is more rapid than when it first affects adults

Heredity—Familial gout affected 22 to 81 per cent of patients in five English series but only 7 to 12 per cent in five America series More thorough inquiry might raise the latter percentages

Race and Climate—Gout occurs mostly in temperate zones It is common in England and France less common but increasing in North America Hebrews often are affected prosperous American Negroes occasionally

Food and Drink—This is discussed later

Occupation—Commonly affected are those in occupations favored by the well to-do (lawyers clergy, physicians) or those which permit gastronomic indulgence (inn keepers brewers)

Morbid Anatomy—The specific histologic features of gout are best demonstrated by the Galantha method which utilizes absolute alcohol as a fixative and silver nitrate to stain the urates Specific lesions consist of urate deposits in articular periarticular, and sometimes in renal tissues It is not known when during the course of the disease these deposits occur They have been found as early as a couple of days after the inception of the first acute attack' (Brøchner Mortensen) Articular changes depend on the amount of such deposits their location and the resulting reaction to them They are found in cartilage, synovial membrane perichondrium subchondral bone and bone marrow periosteum the fibrous capsule adjacent ligaments tendons and bursae especially of the olecranon The deposits invoke a foreign body cellular reaction with proliferation of fibrous tissue Cartilaginous degeneration and secondary proliferation of marginal bone (secondary hypertrophic arthritis) may occur, as well as bony destruction (destructive arthritis) Areas of erosion, osseous tophi in subchondral and marginal bone generally appear in time as the result of replacement of bone by urates Synovial pannus formation eventually may invade cartilage to the extent that fibrous or

condition perhaps at their normal expectancy

Irregular Gout—Diagnoses of irregular (as opposed to classic) articular gout are still made by some physicians when arthritis begins insidiously and progresses chronically without complete remissions or tophaceous deposits simply because of supposed familial gout or because of the presence of hyperuricemia (not necessarily gouty) Since provable or tophaceous gout practically never develops that way the evidence supporting irregular articular gout is unconvincing Likewise most diagnoses of visceral or abarticular gout cannot be supported because symptoms are indistinguishable from those of nongouty patients of similar age are not consistently or even commonly present in cases of proved (tophaceous) gout and are not consistently relieved by a gout regimen

Complications of Gout.—The only valid examples of visceral gout are found in the cardiovascular renal system Degenerative vascular disease may complicate late gout and cause death by coronary or cerebral vascular accidents The vascular lesions are nonspecific and contain no tophi but intracardiac tophi have been seen Gouty nephritis and renal colic from urate gravel or stones accompany the second stage of gout in from 10 to 30 per cent of cases and the first stage occasionally Hence suspect gout in cases of acute or chronic arthritis with

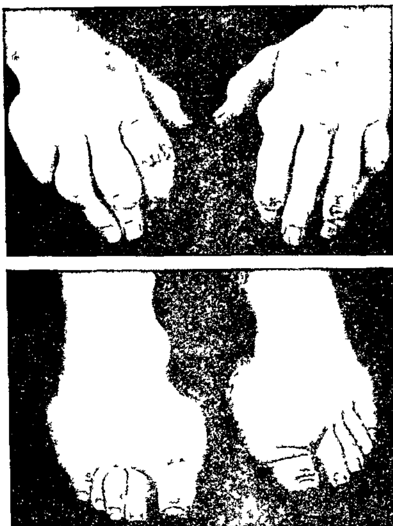


Fig 56—Severe chronic gouty arthritis with ulcerating tophi.

the veins are distended As the swelling subsides the cuticle peels and there is often local itching Another attack perhaps more severe or longer occurs in about a year or perhaps not so soon, it also disappears completely (Fig 55) Sooner or later the disease generally increases in tempo and severity, attacks come semiannually or more often Early attacks are generally monarticular and afebrile, later attacks are often polyarticular and may be febrile (temperature of 102° F or more) Certain roentgenologic changes may appear after several acute attacks and may remain but despite these in this stage of the disease joints recover full symptomless function

shapen subcutaneous tophi are found at various points on the extremities as well as on the ears (Fig 56) Swelling of the olecranon and prepatellar bursae is common The walls of the bursae become thickened and their sacs contain sodium urate In severe cases, there may be marked crippling because of the involvement of many joints

Thus the pattern of classic gouty arthritis can be divided into two great stages comprising four phases (Fig 54) Stage 1 is that of acute recurrent gouty arthritis and stage 2, of chronic gouty arthritis Phase 1 of stage 1 is that of the early, less severe and generally more localized attacks Hyperuricemia may be absent or if present is mild



Fig 55—Acute gouty arthritis of great toe

From five to forty (average twelve) years after the first attack an important change occurs joints no longer recover completely some stiffness pain or deformity remains Thus begins the second stage of articular gout that of *chronic gouty arthritis* The chronically affected joints at first are subject to superimposed acute attacks with incomplete remissions finally exacerbations largely cease and the joints take on the character of the chronic disease In contrast to acute gouty arthritis which is usually monarticular chronic gouty arthritis is nearly always polyarticular the joints of the hands and feet are swollen and mis

or poorly established Phase 2 comprises the later generally more severe and longer attacks which are often polyarticular and associated with more definite and persistent hyperuricemia but are still followed by complete symptomatic remissions Phase 3 (phase 1 of stage 2) is that of early chronic gouty arthritis with acute attacks and incomplete remissions phase 4 (phase 2 of stage 2) is the final relatively painless chronic gouty arthritis Young patients who have active gout may reach stage 2 in middle life Patients who develop gouty arthritis in middle or late life frequently never reach stage 2 but may die of some unrelated

of gout is made only after demonstration of tophi many cases are missed and valuable time is lost

OSSEOUS TOPHI (EROSIONS) —Areas of erosion of articular bone *in gout* represent osseous tophi or replacement of bone by urates (Fig 59) Such tophi are not uncommon in phase 1, fairly common in phase 2 increasingly numerous and large in phases 3 and 4 Areas of erosion caused by replacement of bone by nonuratic debris often occur in rheumatoid or in osteoarthritis and in lupus pernio Hence areas of erosion are not pathognomonic for gout but if they are



Fig 58—Urate crystals from gouty tophus (× 435)

large or numerous they are usually due to gout

Diagnosis in Absence of Characteristic Features—The presence of any characteristic feature (podagra hyperuricemia tophi or erosions) is of great diagnostic import but their appearance is often delayed until rather late in the disease Features more reliable for early diagnosis are the characteristics of the individual attacks and especially the obvious evolution of the clinical pattern of gouty arthritis This pattern (acute recurring attacks complete remissions) is so distinctive as to be almost pathognomonic and permits a diagnosis of presumptive (pretophaceous) gout with no little assurance since it is not exactly mimicked by the other articular diseases which have recurrences and remissions (*e g* rheumatic fever and intermittent hydrarthrosis) When the patient is seen in the first attack with only a fragment of the pattern in view diagnosis is based on certain features of the single attack, no one feature alone is diagnostic but a combination of features is almost pathognomonic of gout

Individual Attacks of Gouty Arthritis Diagnostic Features—PREDISPOSING FACTORS—SEX AND AGE—Among males over



Fig 59—Area of erosion (tophus) distal end of proximal phalanx of great toe

thirty five or forty years of age acute gouty arthritis is the most common form of acute arthritis and should be suspected if gonorrhea and acute trauma are excluded

SEASON—Attacks occur any time but commonly in the spring and fall

OTHER PREDISPOSING FACTORS—These are heredity habitual excesses in food and drink and blood dyscrasias (polycythemia leukemia) involving destruction of blood and liberation of nucleoproteins

PRECIPITATING FACTORS—Common provocatives of gouty arthritis are trauma and dietary indiscretions less common are infections surgical operations certain medicines and psychic upsets Patients rarely

renal colic or nephritis" Very rarely patients may pass urate gravel before the first attack of gouty arthritis

Ulcerating tophi often complicate late gout and may lead to amputation of digits for supposed felons

Diagnosis—Podagra (painful great toe) hyperuricemia subcutaneous tophi and osseous tophi (erosions in roentgenograms) generally are considered of greatest diagnostic value It is commonly believed that the great toe is attacked almost exclusively that hyperuricemia appears early and persists that only a short time elapses between toe and tophus and that evidence of



Fig 57—Two tophi on ear

osseous tophi appears early in roentgenograms These conceptions are largely incorrect

Frequency and Diagnostic Value of Podagra—The metatarsophalangeal joint of a great toe is involved in only about 60 to 70 per cent of initial attacks In some cases it is affected repeatedly in others rarely or never One must not refuse to diagnose gout because podagra is absent

Relation of Hyperuricemia to the Pattern of Gouty Arthritis—The evolution of hyperuricemia frequently *but not necessarily* parallels that of arthritis In the larval or pre arthritic stage symptomless and generally transient hyperuricemia may or may not develop, on rare occasions subcutaneous tophi or urate gravel accompanies it even in this stage Certain Boston students of gout have stated that once arthritis occurs hyperuricemia is present and persistent My experience and that of others contradicts this view In phase 1 of gouty arthritis (Fig 54) hyperuricemia is often present but is frequently absent not only between but during acute attacks In later attacks (phase 2) it becomes more frequent more notable and more persistent In phases 3 and 4 (stage 2) it is almost always present in untreated patients, but under proper treatment it often disappears temporarily The level of blood uric acid does not determine the severity of the arthritis and untreated cases of tophaceous gout occasionally exhibit no hyperuricemia, the normal value for uric acid in the blood is 2 to 4.5 mg per 100 cc (Folin 1930) In summary hyperuricemia is usually present but one must not insist on its presence before diagnosing gout

Evolution and Frequency of Tophi—VISIBLE OR PALPABLE SUBCUTANEOUS TOPHI—These may develop at any stage They are very rare in the pre arthritic stage rare in phase 1 fairly frequent in phase 2 almost always present in phases 3 and 4 when they may be multiple and ulcerating They occur most frequently on ears (Fig 57) and about olecranon bursae and after several attacks they may appear about peripheral joints When tophi are present a diagnosis of tophaceous gout with acute recurrent or chronic gouty arthritis is made when tophi are absent, a diagnosis of presumptive (pre-tophaceous) gout is made on the basis of data to be described later A tophus is not a proved tophus until it has been opened and urate crystals found (Fig 58) Sometimes its identity should be certified further by the murexide test or histologic study

Tophi are found in only about 40 to 50 per cent of all cases They occur more often than this in late or more severe cases less often in early or mild cases The incidence of tophi reported by any physician gives a clue to the accuracy of his diagnostic criteria he is probably too exclusive in diagnosis if tophi are present in 65 per cent or more cases not exclusive enough if they are present in 25 per cent or less But if a diagnosis

useful the administration for a few days of excessive quantities of purines (2.3 Gm daily) and fats perhaps also of alcohol liver extract and ergotamine tartrate Such tests are of limited value As articular vulner ability appears to vary notably from time to time a definite attack may or may not result

Therapeutic tests are more impressive If a stubborn attack promptly responds to colchicine and restrictions of purines and if the disease subsequently is largely or com pletely controlled by a gout regimen, the skeptic will be convinced even without the presence of hyperuricemia or tophi

Roentgenograms—Development of the specific roentgenographic features (erosions or osseous tophi) is governed by the gradient of articular vulnerability and by the number and severity of attacks in any given joint Even in severe gout areas of erosion rarely occur except in feet and hands They appear occasionally in phase 1 commonly in phase 2 and thereafter Periarticular thickening and hypertrophic and destructive changes nonspecific in type may involve affected joints sometimes in phase 1 but generally not until phase 2 and thereafter Roentgeno grams are of limited usefulness in diagnosis characteristic changes are seen rarely in the early generally not until the later phases of gout

Laboratory Data—As stated hyper uricemia is usually present sooner or later but may be absent early in the disease Estimations are generally made on whole blood Jacobson stated that tests made on serum collected under oil were more accu rate serum contains a little more uric acid than whole blood The old argument as to the presence of free and bound uric acid in blood has been reopened by Adlers berg Grishman and Sobotka who studied the uric acid partition of serum by means of ultrafiltration In cases of gout (and also of hepatic damage in nongouty persons) there occurred disturbances of the uric acid partition characterized by a diminution of the free (ultrafiltrable) and an elevation of the bound (nonultrafiltrable) uric acid frac tion in serum Even in certain cases of gout in which the total serum uric acid was nor mal the values for bound uric acid were abnormally high Sedimentation rates may be normal in mild attacks elevated in severe acute attacks and in chronic gouty arthritis Sedimentation rates and values for blood uric acid apparently reflect unrelated factors Hypercholesterolemia may be present Arneth counts may show a left shift

Treatment —The most important point in the treatment of gout is its recognition this done few articular diseases will respond more promptly

Prophylaxis—Children of gouty parents sometimes demonstrate symptomless hyper uricemia such hereditary candidates should live moderately and avoid or undertake cautiously the various provocatives of acute gout as well as occupations conducive to gastronomic overindulgence

Treatment of Acute Gouty Arthritis—Patients who experience monarticular pro dromata or warning articular twinges can sometimes abort attacks by taking a brisk cathartic and from five to ten doses of col chicine ($\frac{1}{100}$ grain or 0 65 mg every two to three hours) The additional use of sodium salicylate (25 grains or 1 6 Gm three times daily) or cinchophen ($7\frac{1}{2}$ grains or 0 48 Gm three times daily) for a few days may be helpful by combating hyperuricemia Patients are wiser to accept such a regimen for a possibly false alarm rather than permit an attack to become established When an attack is established treatment includes the following measures

CATHARTICS—A brisk cathartic (mag nesium sulfate $\frac{1}{2}$ to 1 ounce [15 to 30 Gm] liquor magnesium citrate 6 to 12 ounces [180 to 360 cc] or sodium phosphate 4 to 8 Gm) is supposed to evacuate promptly provocative toxins although empiric its use seems helpful

REST—Affected parts should be com pletely rested preferably in bed and pro tected from bedclothes by a light wooden or metal cradle Weight bearing and activity should not be resumed until pain and tender ness are gone, otherwise an exacerbation may result

HEAT OR COLD—Simple hot water com presses applied every two or three hours are generally effective and often preferable to dry heat compresses of magnesium sul fate or lead lotion are sometimes prescribed Occasionally cold compresses give the most relief

mention them, they must be sought Attacks may be precipitated by such minor trauma as that from a walk of unaccustomed length that incident to excessive sight seeing or to long motoring (pedalling) or that from excesses in golf or amateur labor (lawn mowing) True traumatic arthritis begins immediately after trauma, the inflammatory reaction is in proportion to the severity of trauma is confined to the traumatized region and is not relieved by colchicine the characteristics of gout (history hyperuricemia, tophi) are absent In posttraumatic gouty arthritis the inflammatory reaction is often delayed some hours after trauma is out of proportion to the trivial trauma often progresses to other joints and is relieved by colchicine other characteristics of gout may also be discoverable

Gouty arthritis is often provoked by dietary excesses associated with birthdays weddings, Thanksgiving New Year's Day Passover sales conferences conventions lodge-night Potent provocatives are hunting and fishing trips characterized by trauma and indiscretions around the camp fire (venison meats liquor) Gout however, may affect vegetarians and teetotalers Excesses of purines and alcohol do not cause gout any more than sugar causes diabetes but they may provoke quiescent gout and cause acute gouty arthritis so also may high fat and ketogenic diets used for therapeutic purposes Some attacks seem to be provoked by foods like asparagus not especially rich in purines

Medicinal provocatives include liver extracts although purine free salyrgan, ergotamine tartrate thiamine chloride (vitamin B_1), insulin (rarely) and decholin Lactic acid benzoic acid phenylacetic acid and similar compounds reduce the excretion of urates Transfusion purging and bleeding may provoke acute gouty arthritis When acute arthritis appears under these circumstances suspect gout

Patients with rheumatoid arthritis often feel temporarily better after any surgical operation Exacerbations of rheumatic fever occasionally develop in the second or third week after operation sometimes earlier Acute attacks of gout however, commonly develop within the first seven days after any surgical procedure

Prodromes —Most patients recognize no prodromes some note nausea, indigestion or dyspepsia, melancholia nocturia or polyuria irritability, vague muscular symptoms others experience euphoria and a ravenous appetite

Hour of Onset.—Attacks begin any time frequently in the early morning hours but usually are noted first when on awakening the patient puts foot to floor

Site of Onset —In gout there is a gradient of articular vulnerability whereby distal joints—feet ankles hands and wrists are most commonly affected Knees and elbows are less vulnerable, shoulders and hips are rarely affected except in severe or late gout the spine practically always escapes Olecranon bursitis and tendonitis especially of the Achilles tendon, often occur

Site of Maximal Tenderness —At the great toe maximal tenderness is usually on its medial aspect, not on its top or bottom as in rheumatoid arthritis

Appearance —An affected foot is more often warm and bluish red than clammy cold and bluish white is in rheumatoid arthritis Shiny skin some edema and as the attack recedes desquamation of skin often are notable

Progression of Attack —Attacks may develop slowly but generally develop rapidly maximal disability may appear within twelve to thirty six hours, this is a point of diagnostic significance

Pain —Pain may be mild or moderate but is often excruciating It is not always worse at night

Recovery —Recovery may be slow but is often (spontaneously) rapid occurring within a few days In stage 1 symptomatic articular recovery is complete despite certain roentgenographic residues A man severely crippled for days or even weeks shortly thereafter may recover completely as if never affected this point of diagnostic importance illustrates the comment of Aretaeus A persons subject to gout has won the race at the Olympic games during the interval of the disease

Diagnostic Value of Provocative and Therapeutic Tests —For the doubtful physician or the skeptical uncooperative patient the institution of a provocative test may be

TABULATION

Purine Content of Certain Foods*

List 1 Foods which contain very large amounts (150–1000 mg) of purine bodies in 100 Gm

Sweetbreads	825 mg	Kidneys (beef)	200 mg
Anchovies	363 mg	Brains	195 mg
Sardines (in oil)	295 mg	Meat extracts	160–400 mg
Liver (calf beef)	233 mg	Gravies	Variable

List 2 Foods which contains a larg amount (50–150 mg) of purine bodies in 100 Gm

Bacon beef calf tongue carp chicken soup codfish duck goose halibut lentils liver sausage meat soups partridge perch pheasant, pigeon pike plaice pork quail rabbit sheep shellfish squab trout turkey veal venison

List 3 Foods which contain a moderate amount (up to 50 mg) of purine bodies in 100 Gm

Asparagus bluefish bouillon cauliflower chicken crab eel finnan haddie ham herring kidney beans lima beans lobster mushrooms mutton navy beans oatmeal oysters peas salmon shad spinach tripe tuna fish whitefish

Also whole grain bread and breadstuffs graham bread graham crackers oatmeal crackers rye bread Rye Krisp whole wheat bread Zed

Also whole grain cereals Bemax bran bran flakes cracked wheat Embo graham porridge Grapenuts Krumbles malt breakfast food Pep bran flakes Pettijohns Puffed wheat Ralston's Sims Shredded Wheat Wheaties Wheat oats Wheat worth Whole Wheat Krumbles

List 4 Foods which contain an insignificant amount of purine or no purine

1 Beverages
- Carbonated
- Chocolate
- Cocoa
- Coffee
- Fruit juices
- Postum
- Tea

2 Butter

3 Breads and breadstuffs (except whole grain under list 3)
- Benson's water crackers
- Butter thins
- Corn bread
- Corn sticks
- French bread
- Gluten bread
- Holland rusk
- Soda crackers
- Uneeda biscuit
- Water rolls
- White bread
- Zwieback

4 Caviar

5 Cereals (except whole grain under list 3)
- Breakfast brownies
- Cornflakes
- Cream of wheat
- Farina
- Grits
- Post toasties
- Puffed rice
- Rice flakes
- Rice krispies
- White cornmeal
- Yellow cornmeal

6 Miscellaneous cereal products
- Arrowroot
- Hominy
- Macaroni
- Noodles
- Sago
- Spaghetti
- Tapioca
- Vermicelli

7 Cheese of all kinds

8 Eggs

9 Fats of all kinds (but eat in moderation)**

10 Fruits of all kinds

11 Gelatin

12 Milk
- Buttermilk
- Condensed milk
- Malted milk

13 Nuts of all kind
- Peanut butter

14 Pies (except mince meat)

15 Shad roe

16 Sugar and sweets

17 Vegetables
- Artichokes
- Beets
- Beet greens
- Broccoli
- Brussels sprouts
- Cabbage
- Carrots
- Celery
- Corn
- Cucumber
- Dandelion greens
- Egg plant
- Endive
- Kohlrabi
- Lettuce
- Okra
- Parsnips
- Potato
  - sweet
  - white
- Pumpkin
- Rutabagas
- Sauerkraut
- String beans
- Summer squash
- Swiss chard
- Tomato
- Turnips

18 Vegetable and cream soups (to be made with allowed vegetables and without meat stock)

19 Vitamin concentrates
- Cod liver oil
- Halibut oil
- Yeast

* To calculate the purines or purine bodies in a given food the purine nitrogen is multiplied by 3 example 200 mg of purine nitrogen equals 600 mg of purine bodies

** These foods are high in fat

COLCHICINE.—Colchicine tablets, each 1/120 or 1/100 grain (0.53 or 0.65 mg.), should be prescribed: 2 tablets initially and 1 tablet every two or three hours (in severe cases even during the night) until pain is relieved or gastro-intestinal symptoms (nausea, diarrhea) appear. Having once learned his toxic or "diarrhea dose" (which varies between 6 and 25 tablets, each 1/120 grain [0.00053 Gm.] but is usually about six to eighteen tablets), a patient in subsequent attacks may be able to obtain a satisfactory therapeutic effect without the toxic effect by taking 2 or 3 less tablets in a course. Colchicine is more consistently effective than the wine or tincture of colchicum (dose 15 to 30 minims every two to four hours) which sometimes deteriorates. Gouty patients should carry a few colchicine tablets for prompt use as necessary. It has recently been suggested that the beneficial effect of colchicine may be due to the fact that it lowers the bound rather than the total uric acid titer of blood serum.

NARCOTICS.—Until pain is relieved by colchicine and compresses the preliminary use of codeine (1/2 to 1 grain, 0.032 to 0.065 Gm.) or morphine sulfate (1/6 to 1/4 grain, 0.01 to 0.016 Gm.) may be required.

CINCHOPHEN.—Attacks are controlled better when cinchophen or a substitute for it is used to supplement other measures, especially if hyperuricemia is present; cinchophen should be given during attacks, thus: 7 1/2 grains (0.48 Gm.) three or four times daily with precautions noted hereafter (alkali, carbohydrates, extra fluid).

DIET.—The diet currently approved for acute gouty arthritis is one free of purines, low in fats (which inhibit urate excretion), rich in carbohydrates and in purine-free proteins (milk, eggs, cheese). This diet minimizes the formation of exogenous urates and fosters elimination of endogenous urates. Its rationale may be questioned when one realizes that many patients during attacks excrete urates normally or even excessively. Future work must determine how necessary purine restrictions are during attacks, but then of all times patients are receptive to instruction in those dietary restrictions which the interval treatment of gout seems to require. Complete avoidance of alcohol is advisable.

Interval Treatment of Symptomless Gout.—Gout is not cured when the attack is controlled. Gout is a chronic disease and treatment must be continued in an attempt to prevent or postpone return of symptoms. Contrary to the belief of some physicians that no regimen materially alters the course of gout, most physicians believe that, by adhering faithfully to the interval treatment, many patients can modify the course of the disease, reduce the number and severity of attacks, prevent or reduce the chances of chronic gouty arthritis and avoid or postpone the late and sometimes fatal complications. Thus thirty-one gouty patients who had suffered eighty-four major attacks before adhering to the interval treatment to be outlined thereafter experienced only seven minor attacks during a comparable period of years (Bartels).

CONTROL OF HYPERURICEMIA.—Despite its uncertain relationship to acute attacks, hyperuricemia undoubtedly is important in the production of chronic gouty arthritis, urate gravel and gouty nephritis, hence to combat it dietary restrictions and the intermittent use of urate eliminants should be continued.

DIETARY RESTRICTIONS.—Each patient must be treated individually as the stage and severity of his disease and his temperament dictate. In general the diet should be free of purines on two not necessarily consecutive days and low in purines five days a week. Normal diets contain 600 to 1000 mg. of purines daily; a low purine diet contains 100 to 150 mg. and can be attained roughly by allowing one food from list 2 (Tabulation) one day a week and one from list 3 four days a week, besides whatever foods are desired from list 4. Normal weight should be maintained and obesity avoided. Two days weekly the selections should be only from list 4. Foods in list 1 should always be avoided entirely; also spices, condiments, and rich or indigestible foods and sauces. Deficiencies in protein, iron and vitamin B_1 must be avoided; generally, the diet should be reinforced with an approved preparation of the vitamin B complex. At least 200 international units of thiamine chloride and 200 Sherman-Bourquin units of riboflavin should be given daily; also 5 grains of ferrous sulfate.

neously ascribed to cinchophen are produced by the alkali An alternate method of urinary alkalinization then is necessary

Additional Measures—Contrary to general opinion a few physicians consider colchicine preventative of acute attacks and prescribe $\frac{1}{120}$ grain (0 00053 Gm) three times daily for two or three days each week or for one week each month With similar intent Vorhaus and Kramer gave vitamin B_1 (thiamine chloride 330 to 3300 international units) daily, even though initial doses commonly provoked acute attacks Callahan and Ingham (1939) used this vitamin in the treatment of acute attacks its prophylactic or curative value remains uncertain Of more certain value is the constant avoidance of the provocatives of gout not only the gastronomic but also the traumatic medicinal psychic and surgical provocatives The following regimen generally prevents postoperative gouty attacks use of high carbohydrate purine-free diet and cinchophen or a substitute for five days before and *also* for five days after operation (Hench) Postoperative attacks can also generally be prevented according to Talbott by prescribing daily 2 or 3 tablets of colchicine each grain $\frac{1}{120}$ two or three days before *and* after operation

Treatment of Chronic Gouty Arthritis—This may be prevented by the regimen outlined if not various types of physical therapy are required especially heat to foster resorption of urates Fever therapy or typhoid vaccine has been used occasionally Massage exercise and spa therapy must be used cautiously lest a cure crisis be evoked

Treatment of Tophaceous Ulcers—Large tophi on hands and feet may ulcerate and partially heal only to break down intermittently sometimes discharging urates for months occasionally they become infected Hence tophi in which ulceration is present or impending should be excised When debridement is done thoroughly prompt healing usually occurs Unless the tophus be small it is best before removal to institute the regimen for the prevention of postoperative gouty arthritis

Treatment of Renal and Other Complications—Gouty nephritis has certain distinctive clinical features Its treatment involves a generous intake of fluids (2 to 3 liters daily) restrictions of protein as necessary and continued efforts to combat the underlying gout Prevention of gouty calculi by urinary alkalinization was mentioned Non opaque to roentgen rays such calculi are usually small and pass without surgical intervention There is no specific treatment for the cardiovascular complications of gout

Prognosis, Results of Treatment.—Prognosis is best for those who develop gout late in life poorest for those with symptoms early in life Some patients have mild gout for years only symptomatic on rare occasions after special stress Patients after instruction may *fail* to *control their* gout because of half hearted application of the regimen (the most common reason) because their gout is uncontrollable by diet alone because of occupational or other trauma the unwitting use of medicinal provocatives or because of the presence of some chronic aggravating infection blood dyscrasia or metabolic fault (unsuspected diabetes or thyroid dysfunction) The correction of these factors usually results in improved control of the disease Cases of truly irreversible gout are not as common as supposed

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Coffee and tea are permissible Veterans of gout insist that they can consistently tolerate certain alcoholic drinks but not others, since they cannot agree on which are harmless, the gouty novice should avoid all alcohol unless prepared to pay the price of personal experimentation

Physicians who espouse the allergic hypothesis consider the avoidance of purines less important than the avoidance of foods to which (regardless of their purine content) patients may be individually allergic as suggested by skin tests or by their apparent provocative effect The rationale of such restrictions is not yet clear but physicians should cater to established idiosyncrasies

Urate Eliminants —For the many patients who cannot control symptoms or hyperuricemia by diet alone the additional use of some urate eliminant is required Cinchophen seems to me to be the most effective and there is no exact substitute for it but because of its occasional toxicity it seems desirable first to try a substitute Salicylates augment urate excretion but generally have been considered inferior to cinchophen and ineffective except as mild analgesics unless large irritating doses are used But Jennings recently has concluded that salicylates are as effective as cinchophen in controlling pain and hyperuricemia He prescribed sodium salicylate 80 grains (5.3 Gm) daily, and sodium bicarbonate 120 to 150 grains (8 to 10 Gm) daily, three or four days a week to be continued indefinitely as interval therapy I have found this regimen very useful and generally but not always effective Others prescribe aspirin 60 to 80 grains (4 to 5.3 Gm) daily four days a week Another scheme based on Quick s report (1933) that glycine (amino acetic acid) augments the uricosuric' action of salicylates is this sodium salicylate 60 grains (4 Gm) and amino acetic acid 150 grains (10 Gm) daily three consecutive days a week

If the disease is not satisfactorily controlled by diets and these drugs I believe the intermittent use of cinchophen is justified except for those patients who are unwilling to accept the slight risk or have an idiosyncrasy to it The plan of Graham is generally used cinchophen 7½ grains (0 48 Gm) three times daily for three consecutive days each week The drug is used indefinitely but the dose is reduced or the drug withheld temporarily as control of gouty symptoms and of hyperuricemia permits If the blood uric acid becomes normal or nearly so the drug may be given for awhile only one or two days weekly in the usual dose or in smaller doses three days a week

Whenever cinchophen is given certain precautions such as ingestion of about 2 liters of fluid daily and of liberal amounts of carbohydrates must be taken Cinchophen carries a definite risk which some physicians never condone but which most students of gout consider justifiable if gout is uncontrolled otherwise Serious toxemia from cinchophen is after all rather rare especially in gouty patients The chances of serious or fatal intoxication from cinchophen in gouty patients are believed to be only a fraction of 1 per cent This risk must be contrasted with that of the disease itself in 10 to 15 per cent of cases gouty nephritis develops which is sometimes fatal and the incidence of renal colic from urate gravel and of cardiovascular lesions is notable Since the disease thus carries a much greater risk than its treatment by cinchophen it seems justifiable to assume the small risk of the latter *when necessary* to try if possible to prevent the articular renal and vascular consequences of gout Patients should be told of the risk of cinchophen toxemia and instructed to report such unusual symptoms as anorexia dyspepsia nausea loss of weight pruritus and jaundice to stop taking the drug at once and to report for special therapy consisting of administration of carbohydrates intravenously a high carbohydrate diet vitamin supplements and so forth

Alkalies —When urate eliminants are prescribed patients should take enough alkali to insure constant urinary alkalinity and thus prevent renal colic from the precipitation of urate gravel or stones in acid urine Patients can be taught to test the urine with litmus paper to determine the amount of alkali required this varies somewhat but potassium citrate 15 to 30 grains (1 to 2 Gm) three times daily or sodium bicarbonate 30 to 60 grains (2 to 4 Gm) three times daily generally suffices Occasionally gastro intestinal symptoms erro-

disposed subjects the disease may develop without the occurrence of any unusual provocation as in the case of an apparently normal child In subjects less strongly pre disposed contributing or provocative factors may play a role of greater or less importance according to the degree of the inherited weakness or predisposition

Heredity—Multiple incidence of diabetes in families has attracted attention for cen turies The percentage of families of diab etics in which it is possible to find other affected members varies with the material and method of study With the ordinary run of hospital cases it may range from 7 to 16 per cent In conditions more favorable for the procurement of data over longer periods of time higher figures are obtained e g Jos lin (2669 cases 1925–1928) 25 6 Barach (1030 cases), 44 5 John (630 cases 1939) 35 7 Lawrence (5 462 cases) 32 3 per cent (cited from Joslin) In families of 151 diab etic children who had survived the disease for fifteen years Joslin found an incidence of 52 per cent in 1940 (later 60 per cent) Studying the ratio of affected to nonaffected members in families of juvenile diabetics Priscilla White found 6 7 per cent as against 1 2 per cent in families of nondiabetic con trols In general harmony with the statistics of Umber Cammidge and Kern Berg and White have also observed that when the dis ease has appeared in one member of a pair of similar twins it has appeared in the mate in 65 and 63 per cent of cases as against 22 and 7 per cent in comparable pairs of dis similar twins When it is recalled that po tential diabetics may die before the disease appears or be yet unborn or may be living with an undiscovered diabetes when the his tory is taken such data lend color to the proposition that the disease is inherited or susceptible of transmission in every case

ANTICIPATION—It has long been known that when diabetes occurs in two or more members of the same generation of a given family it may develop in all in the same period of life There are striking exceptions in a minority group but in the majority of my cases the ages of onset have fallen within a span of fifteen years It was also observed by Bence Jones Gruber and Niessen (1865–1897) and later by Naunyn (1906) that when diabetes occurs in father and son it may appear at an earlier age in the son than in the father The same phenomenon may occur in uncle or aunt and nephew or niece and repeat in the following generation Thus the disease may appear in a first generation in the forties fifties or later in a second gen eration in the forties, thirties or twenties, in a third in the first or second decade The phenomenon is known as *anticipation* In 100 families that exhibited the disease in two or more generations Woodyatt and Spetz found evidence of the trend definite in 79 probable in 85 possible in 90 absent or reversed in 10 per cent The difference be- tween the ages of onset in two succeeding generations varied from less than five to fifty years but the average (in 90 cases) was twenty years When the trend occurs it leads in the course of two to four genera- tions to the appearance of the disease in childhood or youth and in such cases the juvenile diabetics are fruits of a *family* diab etes that has already existed in one or more *preceding* generations As a continuation of the trend to progeny of such juvenile diab etics would bring the age of onset into pre- natal time (diabetes *in utero* or nonconcep tion) the question arises as to whether diabetes is not a self limited disease which runs its course in a given family and tends to extinction in a limited number of generations

MENDELIAN RATIOS—Hereditary phe nomena are too numerous and complex to be fully explained by any known laws Whether diabetes is transmitted on men delian lines and if so as a recessive or domi nant trait is a much discussed theme On the basis of data on 851 families of diabetic children Pincus and White support the con ception of simple recessiveness in the men delian sense The theory implies that if two parents are diabetic or potentially so 100 per cent of their children will develop the disease if they live long enough if one parent is diabetic and the other a carrier 50 per cent if both are carriers 25 per cent if one is normal and the other a carrier 0 per cent (but then all would be carriers) The incidence found in children of crosses of the three types were less than the expec tancy in every case but with corrections for five possible sources of error on the basis of probabilities derived from statistics and on the assumption that both parents of any

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DIABETES MELLITUS

Definition—Diabetes mellitus is an inheritable constitutional disease of unknown cause characterized by continuing hyperglycemia and glycosuria and in the more advanced stages by acidosis (*ketosis*) These signs are expressions of disturbed relations between chemical changes of carbohydrate protein and fat in the body and especially those that produce or consume sugar and the acetone bodies Of the many factors involved in the equilibrium of these reactions in normal conditions the particular ones of the greatest interest in this disease are the hormones of the islets of Langerhans the anterior pituitary and adrenal cortex the two latter increased and the former diminished in the relative sense It appears however that a deficiency of insulin (relative or absolute) is to be considered as the basic determining factor The disease is further distinguished especially in the middle and later decades of life by arterial changes (*arteriosclerosis*) and a variety of other manifestations not directly relatable to the hyperglycemia, glycosuria etc

History—Allusion to polyuria occurs in records of great antiquity The name diabetes—from the Greek (διαβαίνειν to run through διαβήτης siphon)—appears in a work of Aretaeus (first century A. D) The polyuria according to Galen was due to a state of the kidneys like that of the bowel in diarrhea, which permitted drink to pass through the body without alteration In the Occident this doctrine still survived at the end of the fifteenth century The sweet taste of the urine was known in India as early as the fifth or sixth century A thousand years later it enlisted the interest of Thomas Willis in England (d 1675) and in 1775 Dobson evaporated diabetic urine and recovered a sugar This was identified with the sugar of grapes (glucose) by the chemist Chevreul in 1815 After Dobson s discovery Cullen distinguished the two conditions known thereafter as diabetes mellitus and diabetes insipidus respectively and Rollo treated a famous case by "a diet of animal food as rancid as possible with the view of preventing fermentation of sugar in the stomach" Between 1849 and 1877 Claude Bernard developed his original concept of the liver as the site of sugar production and of diabetes as due to an overproduction of sugar in the liver (*glycogenic theory*) In 1889 to 1892 von Mering and Minkowski proved that extirpation of the pancreas invariably results in diabetes and that the pancreas produces an internal secretion necessary for the *normal metabolism* of glucose It was not until 1921 that Banting and Best in the laboratory of McLeod prepared extracts of the pancreas that could be proved to contain the active principle known thereafter as *insulin* A new chapter in the history began in 1930 with the observation of Houssay that hypophysectomy markedly alters the manifestations that ordinarily follow pancreatectomy Whereas the latter alone leads to hyperglycemia glycosuria, acidosis and death in dyspneic coma—animals from which both glands have been removed show less hyperglycemia and glycosuria and also little or no acidosis In fasting the glycosuria disappears and the animals die in hypoglycemia Long and Lukens observed similar pictures in pancreatectomized adrenalectomized animals It was then demonstrated by Young in 1937 that it was possible to produce permanent diabetes in dogs by the administration of extracts of the anterior lobe

Etiology—Injuries and diseases of known etiology effecting the destruction of a sufficient portion of the pancreas account for a small proportion of clinical cases of diabetes When recognized these are classified under the heading of *pancreatic diabetes* as in contradistinction to *pure (or spontaneous) diabetes* The cause of the latter is not known It is clear however that etiologic factors of decisive importance are susceptible of hereditary transmission Naunyn favored the conception of diabetes as the expression of an *individual inherited disposition* having its seat in the nervous system (*neuropathic disposition*) According to this view in sufficiently strongly pre

diabetes in a not inconsiderable fraction of cases The same is true of psychic shocks and severe emotional disturbances Depressive emotions anxieties fears unhappiness arising from various causes—such as domestic infelicities financial losses etc are notoriously capable of provoking the onset Various injuries and diseases of the central nervous system such as concussions skull fractures apoplexies brain tumors etc may produce a glycosuria which proves to be transient and not diabetic or may serve to provoke the onset of true diabetes

Infections.—The onset of diabetes often occurs during or after an acute infection In 1918 and 1919 many of the new cases of diabetes appeared during or after influenza But in proportion to the incidence of influenza diabetes was rarely a complication Certain types of acute upper respiratory tract infections that prevail at some seasons are more potent than others to aggravate an existing diabetes or provoke its onset Generally speaking any infection may aggravate a diabetes Very mild forms of diabetes may be brought to light during an attack of tonsillitis sinusitis cystitis cholecystitis etc and disappear with the cure of the infectious process Chronic infections may contribute to the maintenance of glycosuria Infections that lead to pancreatitis may produce pancreatic diabetes But there is no substantial support for an infectious theory of true diabetes The observation that the tolerance of a diabetic may improve in the course of tuberculosis recurs in the literature

Syphilis—Syphilis plays no important role

Morbid Anatomy—As early as 1788 Cawley reported stone and atrophy of the pancreas in a case of diabetes and the repeated findings of morphologic changes was one of the clues that led to Opie s establishment of the relation of the islets of Langerhans to diabetes

The following tabulation condensed by Lukens from a table of Warren s with added data on fibrosis shows the lesions of the pancreas that may be found

From these figures it is seen that 80 per cent of diabetics have some island lesions while 20 per cent have been classified as normal and 61 per cent have had some degree of generalized pancreatic fibrosis usually interacinar In nondiabetics of corresponding ages only 16 per cent had any island lesions and only 29 per cent had pancreatic fibrosis (Lukens)

AUTHOR	TOTAL CASES	NORMAL	HYALINE	FIBROSIS	HYDROPIC DEGENERATION	OTHER LESIONS	GENERAL PANCREATIC FIBROSIS
Cecil	90	11	27	49	0	3	67
Waller	29	8	4	12	0	5	
Gill and Logan	142	11	30	79	0	22	
Herxheimer	97	22	38	13	0	0	
Warren	484	127	200	1 9	22	133	269
Total	842	179	299	232	22	163	

Since the discovery of experimental pituitary diabetes Lukens and Dohan and others have studied the evolution of islet lesions in this condition from primary swelling and hydropic change to ultimate fibrosis or disappearance and a reversal of the process under appropriate measures (discontinuance of pituitary administration of insulin) before the fibrotic stage is reached

Changes in other endocrine glands besides the pancreas are often found in autopsy material but none are established as constant or distinctive at the present time Eosinophile or basophile pituitary adenomas in acromegaly or Cushing s syndrome are often associated with diabetes but are absent in most cases Diabetes may be associated with adrenal tumors but changes in the adrenals have been missed in most cases

Atherosclerosis or *atheroma* are constant after the third decade of life Warren Root, *et al* found evidence of it in earlier life At any particular period of life the aging of the arteries of a diabetic may be 10 per cent greater than in the average normal person (H E Eisele)

Physiology—Glucose is continually entering the body from the food and tissues continually undergoing chemical change and elimination If S is the rate of glucose *supply* from all sources C the rate of *chemical change* E the rate of *excretion* and B the *body content* then in normal conditions E

diabetic child are carriers (if not actually or potentially diabetic) the figures agree

Overindulgence and Obesity—In India in the fifth or sixth century Suzruta described diabetes as a disease suffered principally by the rich, because of their overindulgence in carbohydrates (rice flour and sugar), and since the end of the seventeenth century this view has recurred repeatedly The association of obesity and diabetes has long been known Of 1000 cases observed by Joslin 77 per cent were overweight as judged by a standard height weight scale It is a well known fact that reducing the weight of an obese diabetic may increase the tolerance for carbohydrate and that tolerance may be lowered by overfeeding In a statistical study of subjects who exhibited glycosuria during tolerance tests, Newburgh observed that about a half were obese and over thirty years of age After the weights of such subjects had been reduced to normal by under nutrition more than 90 per cent were aglycosuric on diets containing 300 Gm carbohydrate and then exhibited normal tolerance curves Abnormalities recurred with recurring obesity and disappeared again with reductions of weight In such cases we are dealing Newburgh suggests with a clinical entity in which the obesity is the principal abnormality and hyperglycemia is a secondary phenomenon According to Long analogous phenomena are observed in experimental obesity in rats The conversion of sugar into fatty acids which is possibly a process that occurs mainly or entirely in the liver (see Utilization) is one of the main means that the body possesses for the disposition of sugar and a large factor in tolerance It would seem possible that as accumulations of fat (especially in the liver) approach a limit the process is retarded It is apparent therefore that obesity may hasten the onset of diabetes in a predisposed subject, aggravate an existing diabetes or lower the tolerance of a nondiabetic These and the high incidence of obesity in diabetics past a certain age are the main supports for the conception that obesity *causes* diabetes However obesity is not common in young diabetics many obese subjects never develop true diabetes and it would seem probable that obesity in diabetic stock is in the nature of associated endocrinopathy

Other Endocrinopathies—Glycosuria associated with hyperglycemia is a common accompaniment of various endocrinopathies and may be produced experimentally with various gland extracts (pituitary adrenal, thyroid etc) *Vice versa*, many patients with true diabetes exhibit evidence of disorders of other endocrine glands besides the islets Some types of obesity may be so considered, also arterial hypertension, impotence in males sterility in females hyperthyroidism hypercalcemia etc In both connections the pituitary is important as well as the adrenals gonads and thyroid The diminution or abolition of the glycosuria and ketosis of pancreatic diabetes that follows hypophysectomy, the diabetogenic and ketogenic activity of certain fractions derivable from the hypophysis, the evidence of pituitary dysfunction among diabetics, and the work of Young showing that a permanent diabetes can be produced by the administration of large quantities of anterior lobe extracts all indicate that in diabetes the pituitary gland is always involved

Arteriosclerosis—After the third decade of life arteriosclerosis is increasingly frequent in diabetics and is found with great uniformity in middle aged and elderly subjects It has been regarded as causative through the production of organic lesions (atrophy of the pancreas central nervous system lesions etc) But the arterial disease of diabetics is often most marked in the mildest cases and absent or insignificant in the most severe forms seen in younger subjects, and can scarcely be viewed as a causative factor

Gout—The association of gout and diabetes has been remarked on in the literature Charcot and his pupils held that the inheritance of a common underlying character could lead to the development of both conditions The writer concurs with the view of Pratt that in this country at least the two are not often associated

Race—Statistical studies generally confirm the view that the incidence of diabetes in Jewish families exceeds that of any others Variations of the incidence in Chinese Japanese Negroes Indians and others are less definitely established

Nervous and Emotional Factors—Severe nervous shocks such as may result from injuries exposures etc precede the onset of

undergoes chemical change parts are disposed of by (1) *direct oxidation* to CO_2 and water (2) *polymerization* to glycogen and (3) *reduction* to fatty acid (and fat)

DIRECT OXIDATION occurs continuously in all the tissues but as the muscles represent the great bulk of actively oxidizing tissue it occurs in muscles on the largest scale With the low rates of supply that prevail in fasting it may account for the disappearance of nearly all the sugar that enters the blood With the higher rates of supply that prevail after meals the rate of direct oxidation rises but it cannot be driven above a normal limit As this limit can be exceeded (2 or 3 1) by the rates of absorption that prevail after meals some fraction of a post prandial sugar supply is necessarily disposed of by other means

POLYMERIZATION to glycogen occurs on the largest scale in the liver It serves especially for the quick disposition of excesses of sugar but has definite limits The glycogen content of an adult liver is rarely as high as 15 per cent Even 7 per cent (*i e* 210 Gm per 3000 Gm liver) is a high normal figure This may approximate half of the total body content When saturation is reached the process stops and glycogen once formed can only be disposed of by reconversion into sugar So glycogen formation while important in the regulation of the blood sugar level can only account for the temporary disposal of a small quantity of sugar that might be stated roughly as about a pound

REDUCTION to fatty acid is also a process that occurs largely in the liver* but unlike glycogen fatty acid can be further metabolized without reconversion into sugar It is susceptible of direct oxidation as such or of storage as fat in enormous amounts with no more than an approach to saturation and such fat can burn like fat derived from any other source So reduction to fatty acid is really a step in a process of INDIRECT OXIDATION and a major means for disposing of continuing high supplies In this connection it should be noted that whether glucose burns directly to CO_2 and water or is first reduced to fatty acid (and/or fat) and then burns as such the R Q for the whole process is exactly the same in either case Studies of muscles of depancreatized animals by tissue slice and similar methods show that they retain the ability to oxidize glucose and suggest that this ability may approach the norm If this is true it would seem clear that the direct oxidation of glucose in the muscles of the diabetic may not be impaired to a sufficient extent to account for the diabetic state Still such observations would not warrant the conclusion that the oxidation of glucose by any or all methods is not impaired and that we must, therefore fall back on the old conception of an overproduction of sugar from fat As stated a large fraction of all the sugar that enters the body may be changed to fat and burned as such by the process of indirect oxidation Even if the capacity for direct oxidation were intact a limitation of the ability to convert sugar to fat could still account for the diabetic state

* Writer s interpretation not beyond debate

Glucose Excretion —The normal urine is never strictly sugar free The percentage of sugar in normal urine is of the same order of magnitude as that in the blood When a physician tells a patient there is no sugar in the urine but too much in the blood he simply means that the urine when tested with a qualitative reagent such as Benedict s or Haines gives a negative test while the blood when examined by a more refined method such as the Folin Wu blood sugar procedure shows more than the normal percentage of sugar But both normal blood and normal urine yield negative tests with the ordinary qualitative test solutions and both show sugar when examined by similar colorimetric methods To clear up a common misconception Benedict proposed the term *glycuresis* to denote the normal and the use of glycosuria to denote an abnormal excretion of sugar

GLYCURESIS —In over 200 000 examinations of twenty four hour urines carried out in the writer s laboratory by the Folin Berglund method for the quantitative estimation of the sugar of normal urine those that have given negative qualitative tests have shown reducing substances equivalent to 0 1 to 1 0 Gm glucose in the vast majority of all cases Negative qualitative sugar tests are at times compatible with excretions as high as 1.5 to 2 0 Gm per day The average normal urine shows 0 2 to 0 9 Gm per day An excretion of 0 9 Gm is

is minimal, C approaches S, and B approaches constancy at a normal level But if S is greater than C, there is an increase of B and (barring simple retentions) an increase of E Abnormal increases of B and E are characteristic of the diabetic state Clinical diabetes could be due theoretically either to an abnormal increase of S from endogenous sources while C remained normal (*'over production'*), or to a depression of C below the normal, while S remained normal (*under consumption'*) The former would necessarily imply a massive production of sugar from fat But any production of sugar from fat in any condition remains hypothetical at the present time and the great weight of evidence favors the view that we are dealing with a depression of some phase or phases of the utilization of sugar

Glucose Supply—The glucose supply is derived from carbohydrate protein and fat either of the tissues or of the food or both depending upon the state of nutrition Thus on maintenance diets it comes from the food on submaintenance diets partly from the food and partly from the tissues and in fasting entirely from the tissues Any carbohydrate that is utilized on the larger scale in the body may be made to appear in the urine as glucose if it is administered to a diabetic and under favorable experimental conditions may be recovered almost quantitatively as glucose Thus any utilizable carbohydrate is either glucose to begin with or capable of conversion into glucose either in the processes of digestion (as in the case of starches dextrins etc) or of the intermediate metabolism (galactose levulose etc) or of both (cane sugar, lactose, etc) It would appear that glucose (or a closely related unstable substance in chemical equilibrium with it) may be the only form of carbohydrate that can be directly utilized on the larger scale in the animal body Thus 100 Gm of utilizable carbohydrate may introduce into the body roughly 100 Gm of glucose *Protein* yields by digestion or in the course of catabolism a medley of amino acids of which some are convertible into glucose Lusk's completely phlorhizinized meat fed dogs excreted glucose and nitrogen in the ratio of 3 65 1 If there were no oxidation of sugar in the body and if all of the sugar that appeared in the urine were derived from the protein contained in the meat and none from fat, this would imply that 100 Gm of muscle protein introduced into the body 58 Gm glucose In totally phlorizinized *fasting* dogs the D N ratio may linger in the neighborhood of 3 1 and then gradually fall to around 2 4 as exitus approaches and similar ratios around 2 8 (the Minkowski ratio) may occur in the fasting depancreatized dog With the same provisos these ratios would imply that 100 Gm of body protein may yield between 40 and 50 Gm sugar It is now known however that the oxidation of sugar is not abolished in these conditions Removal of the hypophysis or the adrenals of depancreatized animals (Houssay, Long Lukens) and studies of isolated tissue slices and so on show that sugar still burns especially in the muscles in so called 'total diabetes And as glycerol is convertible into glucose it is probable that some sugar is derived from the glycerol of neutral fats (which represents about 10 per cent of their weight) So we cannot state the exact quantity of sugar that protein may yield However as the oxidation of sugar in the tissues can only be driven to a normal limit all sugar supplied in excess of a limit may be recovered quantitatively in the urine and it is probable that the Lusk figure (58 per cent) observed in meat fed dogs is more nearly correct than figures obtained in the fasting state For clinical purposes some formula is needed for rough estimations of the available glucose in different mixtures of C P and F In the older equation $G = C + 0\ 58\ P + 0\ 1\ F$ in which G is the quantity of available glucose the protein figure is probably low and the figure for fat is open to some question Empirically however it works out as well as any other that we can state at the present writing

Glucose Utilization—In normal conditions whatever the glucose supply may be it all disappears within the body except for a trace that escapes in the urine A small fraction may be *retained* temporarily as glucose The remainder undergoes *chemical change* If S is the rate of supply R the rate of retention E the rate of excretion and C the rate of chemical change then $S = C + E \pm R$ and when R and E are minimal C approaches S Of the sugar that

phenomena encountered in the study of diabetes

In the blood sugar regulatory activity of the liver alternate storage and hydrolysis of glycogen are the chief factors involved in short periods of time However as stated (see Utilization), conversion of sugar into fatty acids may also be involved although probably not as a reversible process

Body Content of Glucose.—The sugar of the body is almost wholly in a state of simple aqueous solution in the lymph and blood Even the sugar of the cells is mainly in the cell lymph Being freely diffusible it tends to maintain the same concentration in the blood and lymph The concentration in the blood is the measure of that in the plasma lymph The blood sugar percentage × the total volume of the blood and lymph gives a fair approximation of the body content In an average normal subject it may amount to a matter of some 7 to 10 Gm The total quantity is divided between the blood and lymph in proportion to the relative volumes of the two As in clinical circles it is rather customary to consider the blood sugar percentage as a direct indication of the total quantity of sugar in the body it is well to recall that while the total blood volume varies within relatively narrow limits in health and disease the volume of the lymph is subject to much wider variation Even in normal condition the lymph volume is as variable as that of the urine and variations may be enormous in pathologic states Compare for example the total volume of lymph in a dehydrated subject with that of another in general anasarca with perhaps gallons of fluid in the abdomen alone Observed variations of the blood sugar level can only be regarded as in simple direct proportion to the body content when the ratio of the volumes of the blood and lymph remains the same

Ketosis—The three substances β hydroxy butyric acid CH_3 CHOH CH COOH aceto acetic acid CH_3 CO CH_2 COOH and acetone CH_3 CO CH_3 are known collectively as the acetone bodies In normal subjects on diets containing enough carbohydrate only traces appear in the blood and urine but in fasting (usually after the second day) during subsistence on diets sufficiently low in carbohydrate and high in fat and in a number of pathologic states gross quantities appear in the blood and urine As the two acids of the group are capable of causing the same chain of events that follow administrations of mineral acids the condition was first described and was the first to be described as acidosis But to distinguish the anomaly of the fat metabolism from other forms and phases of acidosis the term ketosis is in current use Pollack has suggested ketotic acidosis as a better term as the acetone bodies consist in the main of the hydroxy acid and as their effects are due to the acid groups These substances spring from fats and proteins The immediate precursor is butyric acid CH_3 CH_2 CH_2 COOH (or a closely related 4-carbon group) derived from the higher fatty acids and also from certain amino acids in the course of their oxidative catabolism

It has long been known from Embden s perfusions of surviving organs that ketogenesis occurs mainly or wholly in the liver and from intravenous injections that material quantities of aceto acetic and β hydroxy butyric acids introduced into the blood stream disappear and are doubtless burned As shown by Wilder (1914) it is only when the rate of intravenous injection exceeds a limit that appreciable quantities appear in the urine Stadie s studies of tissue slices by the Warburg method have shown that the muscles are the principal site of the oxidation and that the rate of oxidation in the muscles cannot be driven above a normal limit So the acetone bodies are produced in the liver destroyed in the muscles and when the rate of production exceeds a limit they appear in excess in the blood and urine

As stated above ketosis occurs in various pathologic states *e g* cyclic vomiting or migraine in children milk sickness or eupatorium poisoning in cattle and man in other intoxications and some forms of infection affecting the liver and in diabetes The calorimetric studies of F G Benedict in inanition and fasting show that ketosis first appears in the normal fasting subject when the rate of carbohydrate oxidation and the quantity of glycogen remaining in the body have both fallen to low levels Studies of dietary acidosis by Zeller and others have shown that on isocaloric isoprotein maintenance diets containing different propor

at the upper limit of the norm, of 1 0 Gm or over above the norm These quantities include a fermentable and a nonfermentable fraction The latter seldom exceeds 0 1 to 0 15 Gm The fermentable fraction falls in fasting It may approach 0 in the fasting state but it rises with starch or glucose feedings and (except in cases of alimentary levulosuria) doubtless consists mainly or wholly of glucose After doses of 50 to 100 Gm glucose the excretion curve shows a rise and fall that normally follow the rise and fall of the blood sugar curve (occasionally after a one to three hour lag) The total output for three hours multiplied by 8 *(or for six hours by 4) is usually less than* 1 0 to 2 0 Gm in normal conditions In the carrying out of tolerance tests the excretion should be plotted by a sensitive method as well as the usual blood sugar curve It not infrequently happens that a subject will show an abnormally high and protracted excretion with a normal or doubtful blood sugar curve

GLYCOSURIA —An excretion of 1 Gm sugar in twenty four hours is usually abnormal and if the sugar is glucose we speak of glycosuria In diabetes the excretion may rise from 1 to 200 Gm or more depending on the severity of the case the diet and so on In the most severe cases and especially in the presence of acidosis the glycosuria *may persist in fasting and the* D N ratios may then approximate those of totally depancreatized or phlorizinized dogs In a great majority of cases of human diabetes the glycosuria can be stopped by partial or total diet restriction If when this has been done the glucose supply is progressively raised by successive additions of a fixed increment to the diet the excretion of sugar may at first remain constant or rise very slightly within normal limits But sooner or later one increment causes an abnormal excretion and we speak of having reached a *tolerance limit* Further additions to the diet thereafter cause progressive increases of the glycosuria until a point is reached at which all of the last increment appears in the urine (*utilization limit*) Thus with a glucose supply rising as a straight line the excretion curve may remain nearly level or rise very little to a certain point and then show a progressive upward trend This type of curve is characteristic of true diabetes In *renal glycosuria* and *glycosuria of pregnancy* there is no definite break in the excretion curve—the output of sugar representing very nearly the same percentage of any supply that may be given There are cases of diabetes in which the critical point in the excretion curve is ill defined and also the acceleration of the sugar excretion after the tolerance has been overstepped These have been referred to as cases with flexible tolerance limits' or 'renal factors etc As the glycosuria shows less than the usual variation with high and low diets and insulin doses they are sometimes attributed to *insulin resistance But all phenomena en*countered in diabetes are not explainable on the basis of ups and downs of the insulin secretion We must also consider other factors and especially disorders of the *regulation* of blood sugar levels (See Blood Sugar Concentration)

Blood Sugar Concentration —In normal subjects the concentration of sugar in whole blood varies in fasting from 0 06 to 0 12, average 0 1 per cent (100 mg per 100 cc) After a dose of 50 to 100 Gm glucose it rises and commonly reaches a peak at 0 12 to 0 17 per cent within the first *hour and* falls to or *below* the original level within two hours The fall of the blood sugar may occur in the course of continuing absorption *and is evidence of the operation of a blood sugar regulating mechanism* The work of Mann Soskin and associates with hepatectomized animals and isolated livers shows that this mechanism resides in the liver and that the liver is set to store or secrete sugar as the blood sugar level rises above or falls below a definite norm In accordance with this view an elevation of the blood sugar to a certain level above the norm *stops* secretion and starts storage of sugar by the liver while a fall of the blood sugar to a certain level below the norm reverses the process In health the mechanism is set to maintain the concentration of sugar in the blood at levels within the normal limits But in abnormal conditions it may be set to maintain a hyper or a hypoglycemic state or become so deranged that it fails to regulate the blood sugar level *This conception is important for the interpretation of blood sugar curves variations in tolerance and other*

to precede it and perhaps contribute to its development As shown by Priscilla White 90 out of 100 diabetic children were above the average in height before the onset of diabetes A certain number of patients give histories of having gained weight rapidly in the period preceding the onset of glycosuria Thus a woman who had never weighed more than 115 pounds up to the age of thirty eight gained 18 pounds in her thirty ninth year for no apparent reason as she was a housewife who lived at home and had not changed her habits or daily routine She then suddenly developed a severe diabetes Males may show the same phenomenon Some patients show evidences of the neuro pathic disposition before the onset of glycosuria A certain physician who was tall and rugged and had weighed 180 pounds became diabetic at twenty six This patient insisted that he was aware of a constitutional change two years before the appearance of glycosuria At twenty four he had become unaccountably nervous irritable depressed fatigable and unlike himself This had led to repeated physical examinations in which nothing abnormal was found in the urine In some cases symptoms of hypoglycemia antedate glycosuria or alternate with it However all such symptoms are indeter minate and it is not possible at present to diagnose diabetes before the occurrence of glycosuria

Diabetes Decipiens —This name is applied to diabetes without any of the cardinal symptoms other than glycosuria It may exist for indefinite periods However even a slight glycosuria with the attendant hyper glycemia may cause subjective sensations Diabetic patients who are accustomed to keeping the urine sugar free by diet and insulin not infrequently know when they are passing sugar by various sensations—such as feelings of pressure over the eyes head aches neuralgias tiredness etc

Commoner Symptoms —The classic symp toms of diabetes are excessive thirst and water drinking (*polydipsia*) the voiding of excessive volumes of urine (*polyuria*) which ordinarily implies increased frequency of urination as well excessive appetite and eating (*polyphagia*) *loss of weight* and general *weakness* Other very common symp toms are *itching of the skin balanitis* or *vulvovaginitis constipation, somnolence dimness of vision* and *muscular pains* Acid osis with acid intoxication leads to the appearance of additional symptoms forming a definite group by themselves A great variety of other symptoms or complications associated with changes in the arterial and nervous systems occur with increasing fre quency after the age of thirty years Some of the commoner of these are *impotence loss of the tendon reflexes neuralgias neuritis perforating ulcer* (*mal perforant*) *cataract diabetic retinitis obliterating angiitis gan grene of the extremities*

Polydipsia —Glucose like salt and other freely diffusible water soluble substances has an affinity for water An excess of glu cose in the body creates a demand for extra water which may be felt as thirst and met by an increased water intake The introduc tion into the body of an excess of sugar results in a shifting of water from the cells to the lymph and blood causing relative tissue dehydration and the symptom thirst

Polyuria —The movement of sugar through the body and into the urine in the form of aqueous glucose solution involves the movement of more or less water In ex periments with continued intravenous injec tions of glucose into dogs the highest urinary sugar concentrations observed by the writer and Hannah Felsher have been between 12 and 13 per cent These concentrations were only observed with marked dehydration of the body The literature contains reports of the same (and even higher) concentrations in diabetes With concentrations of 12 to 13 per cent the elimination of 1 Gm of sugar entails the excretion of not over 6 25 to 8.5 cc of water During intravenous glucose injections the urinary sugar concen tration frequently rises to 8.5 to 9 per cent and may remain persistently at this level only exceeding it when the body has lost sufficient water These latter concentrations are not rarely observed in diabetes and imply the excretion of not over 11 to 12 cc of water per gram of glucose Thus even the excretion of 20 to 30 Gm of glucose does not necessarily increase the urine volume output by more than 240 to 360 cc In cases of relatively mild diabetes in which the power is retained to utilize considerable quantities of glucose and in cases of severe

tions of carbohydrate and fat, ketosis first appears when the ratio of fat to carbohydrate calories approaches the neighborhood of 0 1 or when the Gm of fat, carbohydrate and protein are in about the proportions $F = 2C + 0.5P$ as stated by the writer This is true of the average normal subject variations occurring in various physiologic and pathologic states (pregnancy child hood, some forms of obesity and so on) In fasting and dietary acidosis the administration of small quantities of carbohydrate (50 75 100 Gm) is often sufficient to stop the process and this raises the question as to how carbohydrate exerts its antiketogenic effect There are a number of views

1 The older view to the effect that fatty acids are susceptible of oxidation in more than one way that the oxidation of a given quantity of fatty acid may yield different quantities of acetone bodies in different conditions and that sugar in the course of its oxidation affects the character of the fatty acid oxidation While the oxidation of sugar may spare the oxidation of a calorically equivalent amount of fat and thus diminish ketosis by lowering the magnitude of the fat metabolism it has in addition a specific antiketogenic effect It has been believed for a long time that while alcohol may lower an existing ketosis in some conditions still calorie for calorie it is less effective than sugar The experimental basis for this belief has not been reviewed in recent times However alcohol was much used in the treatment of diabetic acidosis in the pre insulin era and with some success but less than would be expected if alcohol were as antiketogenic as sugar One hundred Gm alcohol a glass of whiskey a moderate high ball once in six hours are the caloric equivalent of 175 Gm sugar an amount which if burned is sufficient to bring most patients out of coma But alcohol never solved the coma problem

2 The view of Stadie that the oxidation of a given quantity of fatty acid produces the same quantity of acetone bodies in different conditions, that the oxidation of sugar spares the oxidation of its caloric equivalent in fatty acids and has no other antiketogenic effect In other words ketosis depends in the main on the absolute magnitude of the fat metabolism As some of Benedict's subjects in fasting acidosis burned in the neighborhood of 2.5 Gm. fat per Kg per day this figure may be taken as an indication of the absolute magnitude of the fat metabolism which is sufficient to determine acidosis in accordance with this view

3 The view represented by Mirsky and Soskin that the antiketogenic action of carbohydrate is not due at all to its oxidation but to its presence as glycogen in the liver It may be noted however that conditions existing in a glycogen filled liver are scarcely compatible with diminished oxidation In accordance with the old view it would be the oxidation of sugar that occurs in the liver (not in the muscles) that exerts the antiketogenic effect, as pointed out by the writer in 1915 but not emphasized in Shaffer's development of the theme

Acidosis.—In the course of a ketosis large quantities of acid enter the system from endogenous sources In the fasting ketosis some 10 to 15 or 20 Gm may appear in the urine in twenty four hours In diabetic ketosis the quantity may rise to 30 50 100 or in some cases 200 Gm or more A minor part of this acid is excreted in a free state A second fraction combines with ammonium and appears in the urine as ammonium salts increasing the ammonium content of the urine (normal 0.5 to 1.5 abnormal 2 0 to 4 0 or even 7 0 Gm in twenty four hours) The balance combines with bicarbonates contained in the plasma lymph and appears in the urine as salts of inorganic base For the disturbance of the acid base balance etc see the chapter on *Acidosis* We may simply repeat here that in normal conditions the total combined plasma CO_2 varies around 60 volumes per cent falling to as low as 8 to 10 in extreme acidosis

Clinical Symptoms and Signs—*Preglycosuric Manifestations*—Before the appearance of glycosuria *diabetes* can scarcely be proved to exist Still in a certain percentage of cases symptoms or signs of abnormality may precede the appearance of glycosuria and raise the question as to whether they should be regarded as preglycosuria manifestations of the underlying disease or merely as those of some other disorder not specifically related to diabetes but which happen

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diabetes on insulin treatment *very considerable glycosuria may occur without abnormal diuresis* As pointed out by Lusk Fisher and Wishart, *sugar in the process of burning or storage tends to hold water in the body* as against the diuretic action of sugar that escapes oxidation and storage Very often however the output of water per gram of sugar rises much higher than 12 cc and with even moderate glycosuria the urine volume may be 3 or 4 liters in twenty four hours and with high sugar outputs 5 liters and upward Outputs of 10 to 12 liters occur but are exceptional Reports in the literature of excretions of 20 liters and over are not beyond bounds of possibility (Under intravenous injection of glucose dogs weighing 10 kilos may excrete 300 cc per hour *i e* at the rate of 50 liters per 70 kilos per twenty four hours)

POLYPHAGIA —When the fuel value of the diet minus that of the sugar lost in the urine is insufficient for maintenance this commonly leads to hunger and an increased consumption of food However various factors—psychic nervous toxic etc may reduce the appetite The onset of acid intoxication commonly leads to anorexia or nausea

LOSS OF WEIGHT —Losses of weight in diabetes are due in the main to undernutrition Such undernutrition may be due wholly to losses of energy corresponding to the sugar excreted in the urine Such losses of weight are to be differentiated from those that are caused by diet restrictions and those that are attributable to losses of water The discovery of a diabetes (or an innocent type of glycosuria) may lead the physician or the patient himself to limit the diet enough to determine a loss of weight when a lesser loss or none at all would have resulted from the disease Also in cases of suddenly developing severe diabetes with polyuria the output of water in the urine may for a time exceed the intake as water formerly held in the tissues is shifted into the blood and urine leaving the tissues in a state of relative dehydration And thereafter even with the reestablishment of a water balance the tissue water may not return to its former level so long as the hyperglycemia persists The same phenomenon may be observed when a severe but controlled diabetes is thrown out of control by a complication or insulin omission In such cases control of the diabetes may lead to the opposite phenomenon the intake of water exceeding the output and the body weight rising Similar fluctuations of weight may occur during the development and resolution of edema

WEAKNESS —Moderate degrees of fatigability may develop with hyperglycemia More marked weakness appears with undernutrition The extent of the weakness may parallel that of the undernutrition Peripheral neuritis and degenerative lesions in the spinal cord may also cause weakness often most marked in the lower extremities *The appearance of weakness in a diabetic who has not been weak before or an increase of weakness in one who has is a characteristic and constant early symptom of acid intoxication* The occurrence of this symptom should always lead to an examination of the urine with ferric chloride

PRURITUS —Generalized itching of the skin occurs more often in advanced cases with marked diuresis emaciation and dryness of the skin than in beginning diabetes It is not very common and usually disappears with control of the diabetes Itching of the genitalia and of the skin of adjacent parts is a much commoner symptom It is generally due to balanitis or vulvovaginitis or to dermatitis or both and is often the first indication of diabetes These affections of skin and mucous membranes which have been attributed to the irritating effects of sugar are rather of mycotic origin The mucous membranes become *reddened* swollen and covered with patches of fibrinous exudate The process may lead to phimosis in the male and in females at times to phlegmonous vulvitis or furunculosis of the labia When dermatitis occurs the parts chiefly affected are the groins the inner surfaces of the thighs the internates axillae and inframammary regions But lesions may appear elsewhere as between fingers and toes in the corners of the mouth etc The skin becomes reddened swollen and sometimes scaly In similar lesions in nondiabetics Finnerud states that of the yeasts or yeastlike fungi that may be responsible those most commonly found belong to the group of monilia (*Oidium albicans*) and that in cases without mucous membrane involve-

ment the cryptococcus appears to be the next most frequent offender Hesseltine reports the recovery of fungi in 18 out of 21 cases of vulvovaginitis in diabetics With control of the glycosuria the disorder usually disappears but sometimes persists and requires special treatment In such cases paintings with a saturated solution of pyoktanin blue (gentian violet) are probably of the most service whether the lesions are on the skin or the mucous membranes

CONSTIPATION —Beginning diabetes with marked glycosuria is often attended by constipation Whether it is due to nervous factors or to the diversion of water from the bowel it usually disappears with control of the diabetes and the establishment of a diet containing a normal proportion of vegetables and fruit

SOMNOLENCE —With hyperglycemia and glycosuria patients often complain of feeling drowsy or dozing after meals Perhaps this symptom is due to internal redistribution of water The possibility has also been suggested that glucose itself as an alcohol may exert some soporific effect *Somnolence is also a symptom of early acid intoxication*

DIMNESS OF VISION —Dimness of vision may be due to refractive changes caused by alteration of the water content of the eye and of the vitreous in particular The refraction may change rapidly with variations of the hyperglycemia glycosuria and diuresis but returns to its original status when the disturbing factors are eliminated In elderly subjects dimness of vision is frequently due to other causes such as cataracts disease of the retinal arteries—so called diabetic retinitis etc In such cases the diabetes itself may have little to do with the course of the symptom In the latter type of visual defects the lesions are found by examination

IMPOTENCE —This is a common symptom often observed in well nourished or obese individuals with mild diabetes after the third decade of life The sex power is said to return in some cases with disappearance of the glycosuria It is not necessarily associated with the absence of motile spermatozoa nor with testicular atrophy It is possibly an associated glandular dysfunction This view is supported by increasing evidence of pituitary dysfunction

SYMPTOMS REFERABLE TO THE NERVOUS SYSTEM —A great variety of nervous symptoms may occur in the course of a diabetes

LOSS OF THE PREPATELLAR TENDON REFLEX —According to Rosenstein Grube and Naunyn this appears in 20 to 30 per cent of cases De Renzi found the knee jerks normal in 2 weak in 10 and absent in 38 out of 50 cases The symptom is rare in young individuals Some improvement may follow adequate treatment of the diabetes Autopsies may reveal no morphologic changes in the peripheral nerves or spinal cord but degenerative lesions have been observed in the posterior columns Exaggeration of the knee jerks is not incompatible with diabetes

MUSCLE PAINS —Muscular weakness which is one of the classic symptoms of diabetes may be associated with aching or pains in the muscles with little or no tenderness on pressure and this is sometimes observed in the mildest cases suggesting a possible neuritic factor This symptom is to be distinguished from *muscular cramps* that cause severe pain and tender swellings These may also occur with mild diabetes and arteriosclerosis but are more often observed with severe glycosuria and polyuria Of the *neuralgias* those of the sciatic nerve and brachial plexus are the most common although any nerve may be involved A modern tendency is to consider these symptoms as manifestations of bursitis fibrositis osteo arthritis focal infections etc which doubtless contribute in many cases as does also the state of the arteries But true neuritis also occurs

PERFORATING ULCER similar to that seen in tabes spina bifida syringomyelia leprosy etc is relatively rare in diabetes It is not due to syphilis Its usual site is on the foot It has been reported in other locations also Its appearance in atypical sites and its healing in some cases have been said to distinguish it from *mal perforant* of tabes dorsalis *True polyneuritis* in diabetes gives rise to a great variety of manifestations not necessarily to be distinguished from those of polyneuritis in nondiabetics The name of diabetic *pseudotabes* is applied to a form of diabetic multiple neuritis with loss of the knee jerks ataxia and muscular weakness The pupils may be contracted and react sluggishly but there is no true Argyll

Robertson pupil The sluggishness of the pupil may be enhanced by sclerosis of the arteries of the iris In some cases degenerative lesions in the posterior columns have been found in conjunction with degenerative changes in the nerves

FURUNCULOSIS —Furunculosis may occur in any stage of diabetes and may be an indication of the disease But it is also common in nondiabetics The existence of an unbalanced diabetes implies a lowered rate of glucose burning in the various tissues including the skin and this may be associated with a diminished resistance to infection This factor may be corrected by suitable treatment of the diabetes Otherwise the pathogenesis course and treatment are those of furunculosis in general A run of boils is often due to repeated reinoculations of the skin so that apart from general measures it is important to isolate any discharging lesion When moist dressings are used a saturated solution of magnesium sulfate has many advantages Avitaminoses should be corrected

GANGRENE —The arterial disease that is characteristic results in thickening of the tunics and narrowing of the lumina of the arteries Occlusion of an artery leads to gangrene Although existent in variable degrees throughout the arterial system the disease is most marked in the lower extremities The blocking of a digital artery or a smaller cutaneous branch causing gangrene of a toe or a superficial area may often be handled conservatively Occlusion may be spontaneous or may be provoked by slight injury or infection It is frequently followed by secondary infection When a larger artery of the metatarsus occludes early amputation is indicated Owing to the fact that the anterior and posterior tibial and peroneal arteries and their branches and anastomoses are all commonly involved in the same general process it is usually preferable to amputate above the knee The state of the arteries that leads to gangrene is not appreciably changed by treatment directed at the diabetes It is often most marked in the mildest cases

DIABETIC XANTHOCHROMIA —Many patients with severe diabetes develop a yellow coloration of the skin a symptom described as xanthochromia The color varies in different cases from a light lemon to a reddish saffron or chrome yellow The staining is often deepest in the skin of the palms and soles The color is due to carotin which occurs in excess in the blood in these cases It is more commonly seen with undernutrition and disappears with control of the diabetes and the establishment of a normal diet. It is associated with an abnormality of the lipoid metabolism and according to Rabinowitch with that of cholesterol in particular

XANTHOMA DIABETICORUM —Diabetic xanthoma is also associated with abnormalities of the lipoid metabolism that may develop in the course of a diabetes and disappear with control of the latter condition The relation between diabetic xanthoma and that which occurs in nondiabetics has not been established

Symptoms of Acid Intoxication —The character and intensity of these symptoms depend in the main on the degree of depression of the alkali reserve and the sequence of symptoms on factors that determine its variation Thus the symptoms may appear insidiously or suddenly advance slowly or rapidly remain stationary for a longer or shorter time or recede depending on variations of the diet the insulin dosage the intake of base the severity of the diabetes and other factors that determine the alkali level With a steadily falling alkali reserve the following are the commonest early symptoms

1 *Weakness* when none has existed before or the accentuation of preexisting weakness

2 *Anorexia or Nausea or Nausea and Vomiting*

3 *Increased Frequency of Respiration*

4 *Dulling of the Sensorium*

5 *Cutaneous Flush*

6 *Acetone Odor on the Breath*

In the earliest stages any or all of these may be inconspicuous The respiration may not be increased except on exertion The color of the face may be hard to distinguish from that due to exposure to wind or sun The acetone odor may not be distinctive But unusual tiredness or willingness to rest and especially a dulling of the appetite symptoms of gastric hyperacidity anorexia or nausea in a diabetic should awaken suspicion In cases exhibiting these milder

symptoms the plasma CO_2 is usually between 20 and 40 volumes per cent

With deepening intoxication weakness progresses the respirations increase in frequency and depth The symptom *air hunger* makes its appearance Nausea and vomiting continue *Pains* may appear of a neuralgic or neuritis like character in one nerve or plexus or more often in several

Abdominal pain—usually epigastric—may be severe and simulate appendicitis or pancreatitis A *leukocytosis* is frequently found The count may rise to 25 000 and over However abdominal pain occurs only in a limited proportion of cases and pain in general is frequently absent Symptoms of *dehydration* are constant *Thirst* is incessant The skin lips tongue and fauces become dry the intra-ocular tension is diminished (soft eyeball) Dulling of the senses and of the mind progresses The patient is frequently somnolent Exceptions occur with urgent dyspnea the patient remaining alert and anxious as he struggles for air The plasma CO_2 is then between 10 and 25 as a general rule

With deep acid intoxication the stormier symptoms—nausea vomiting pain etc subside as the mind and senses become more dulled with developing coma Coma however is seldom so deep that the patient cannot be aroused enough to swallow until shortly before death The following is taken from Kussmaul s description of the comatose patient (1874) There is nothing to show that the air in its passage to and from the lungs has the slightest obstruction to overcome The chest expands freely in all directions The full inspirations are followed by just as full expirations There is no congestion of the veins of the neck no cyanosis These great respirations are further as a rule accelerated The contrast between the general weakness and the strength of the respiratory movements is one of the most striking features of the picture

The urine in coma commonly shows besides sugar acetoacetic acid etc a trace of albumin and many casts Fever is usually the sign of a complication or dehydration After acid production has been controlled the injury done to the tissues during the period of acidosis is not immediately repaired and if irreparable the patient may fail to recover consciousness after the acidosis is stopped or may recover consciousness and die of heart failure The plasma CO_2 is usually between 10 and 15 per cent

The longer an acid intoxication continues the more frequent is the occurrence of complications The prolonged effect of acid on the tissues frequently leads to *dilatation of the heart atony of the muscles of deglutition atony and dilatation of the stomach dilatation of colon anuria* etc

Clinical Course—The clinical course in the individual case is extremely variable There are cases with sudden onset and rapid progress which lead to coma within a few weeks unless active preventive steps are taken Such cases are commonest in childhood and youth A case may begin with all signs of severity and later assume the aspects of mildness or the reverse may occur an apparently mild case becoming severe Generally speaking in a child developing diabetes the major part of the tolerance will have been permanently lost within one to one and one half and in a youth within two to three years of the onset although careful treatment and unknown factors may result in the preservation of the tolerance for much longer periods As a general rule also the greater the age at which diabetes appears the slower will be its subsequent course But many exceptions must be noted Rarely and usually in subjects no longer young a definitely established and long standing diabetes severe enough to require insulin treatment may become mild or disappear temporarily or permanently Whereas many factors capable of affecting the course are known there are still unknown factors of high importance Joslin formerly stated that complete disappearance of a diabetes during life had not been proven in any of his cases and held to the view Once a diabetic always a diabetic Naunyn von Noorden and others believed that cases might recover The diabetes associated with disease of the pituitary is notable in this respect and I have seen cases of *apparent* recovery in the absence of *recognized* pituitary disease (Since the above was written I understand that such cases have also been observed in the Joslin Clinic)

In the section on Heredity we have re-

ferred to the phenomenon of *Anticipation* and suggested the possibility of considering the true course of diabetes as run in a family as distinguished from the individual case The suggestion implies that diabetes may appear in a given family in which it has not been known to occur before and run its course in a limited number of generations (as few as two most often three occasionally four and rarely more) When the disease begins in a given family it first affects persons in the forties, fifties or later, after a generation or two those in the twenties thirties or forties and finally in youth and childhood In accordance with this conception the old diabetic is usually a first generation case and a juvenile diabetic a second third, or fourth generation case and most often a third Well known differences in the course of diabetes in the old and young are *related to the age of the family disease* The old diabetic represents an earlier stage and a young diabetic a more advanced stage in the course of the disease

Clinical Types —The degree of impairment of the power of the body to dispose of glucose is commonly used as the basis for a classification of cases of diabetes as mild moderate or severe However mildness or *severity is not wholly a matter of degree* At the beginning of a diabetes destined to run a rapid course the degree may be slight but the type severe as shown by its progress An inherently mild type of diabetes is one of low or moderate degree manifesting relatively little tendency to progress The diabetes of elderly subjects is commonly of a mild type and pure diabetes in young subjects severe But low grade slowly progressive types of diabetes may occur in the young and even in slowly progressive cases time may determine a loss of tolerance equal to that which occurs more quickly in other cases

Diagnosis —The occurrence of characteristic symptoms such as thirst and polyuria with or without others and the finding of sugar in the urine leave little doubt of the diagnosis Problems arise when positive qualitative tests for sugar in the urine or unusually high blood sugar percentages are found more or less accidentally in the course of a general examination such as a health or insurance examination, or that of a patient whose principal symptoms are those of some other *condition* In such cases a study of the family history the physical type of the patient and of signs that are often associated with diabetes may afford clues of much importance A history of diabetes in the family the inheritance of physical characteristics that are often associated with diabetes such as unusual height stature or obesity, a family history of metabolic or endocrine abnormalities, which if not diabetic may be related to diabetes arteriosclerosis hypertension, renal glycosuria etc, are all suggestive However, proof that a subject is diabetic rests on the demonstration of the characteristic anomaly of the glucose metabolism This anomaly cannot be proved to exist prior to the appearance of glycosuria

Diagnosis of Glycosuria—This rests on *the demonstration of an abnormal quantity of a dextrorotatory fermentable reducing substance in the urine Qualitative Data* A definitely positive qualitative test with one of the commoner copper reagents indicates more than the usual concentration of reducing substance If after the urine has been fermented with yeast it no longer yields a positive test the reducing substance is probably *a sugar If the unfermented* specimen shows dextrorotation and if this disappears with fermentation the sugar is glucose as other dextrorotatory and fermentable reducing substances are not known to occur in human urine *Quantitative Data* As measured by the Folin Berglund method for the quantitative estimation of sugar in normal urine the total output of sugar (fermentable and nonfermentable) by adults on diets consisting of staple foods is commonly found between 0 3 and 0 9 Gm in twenty four hours Even when enough glucose is added to the diet to bring the total glucose supply *to 400 Gm the output is* commonly less than 1 Gm exceptionally 1 to 1.5 rarely 2 to 2 5 Gm The excretion of 1 5 Gm or more is therefore abnormal If a repetition of the determination after fermentation shows a fall of the figures (as to *0 2 to 0 4* Gm) the difference is probably due to glucose With slight sugar excretion the qualitative test may be negative and polariscope readings unsatisfactory In fasting the total sugar excretion is usually less than 0 4 Gm

in twenty four hours or 0 1 Gm per six hour period After a meal or the ingestion of glucose it rises The excretion of 0 4 Gm or more in six hours or of 0.2 Gm in three hours after a glucose feeding (of 100 Gm) is unusual and suggestive

Differential Diagnosis of Glycosurias—The glycosuria of diabetes responds in a characteristic way to diet changes and in sulin With rare exceptions it disappears with sufficient limitation of the diet (with or without insulin) When absent on a given diet (with or without insulin) a rising diet leads to its reappearance when the glucose supply exceeds a limit (any insulin dosage remaining the same) With diets rising above this limit it shows a *progressive* acceleration When glycosuria is present on a given diet it shows characteristic responses to insulin The glycosuria of true diabetes is associated with hyperglycemia In renal glycosuria and innocent glycosurias of pregnancy the blood sugar percentage remains as a rule within normal limits There is then no definable tolerance limit little or no *progressive* ac celeration of the sugar excretion with rising diets and 10 to 20 units of insulin have very little or no effect Thus in a typical case of renal glycosuria the excretion of sugar for three days on a constant diet calculated to introduce into the body 150 Gm of glu cose per day may average x Gm and on a similar isocaloric diet with a glucose equiva lent of 300 Gm the output may average $2x$ Gm or somewhat more the excretion representing the same or nearly the same percentage of the higher and lower glucose supplies In true diabetes once glycosuria has made its appearance the percentage ex cretion rises with even a moderate dietary increase In some types of inherently mild diabetes the tolerance limit is ill defined the response to insulin slight and the accelera tion of the glycosuria with rising diets less striking than that in purer forms Even so a sufficiently high insulin dosage will stop the glycosuria and with diets sufficiently low and high the difference in the percentage excretion is definite Glycosurias other than renal and pregnancy glycosurias whose inno cence is proved in the course of time by their clinical course may be associated with hyperglycemia and may respond to insulin doses But often the dose of insulin required to eliminate a few grams of sugar from the urine is greater than that which might be expected in a typical case of true diabetes and the acceleration of the glycosuria on rising diets is frequently less These consid erations may assist in the differentiation of nondiabetic and diabetic glycosurias *Blood Sugar Criteria* The fasting blood sugar level is usually found between 0 06 and 0 12 averaging 0 1 per cent A fasting blood sugar of 0 13 per cent is suggestive of some ab normality although not necessarily diabetes Most writers agree that a fasting value of 0 17 per cent or over is definitely abnormal and usually due to diabetes in which case there should be no difficulty in demonstrat ing the passage of more than a normal amount of sugar in the urine either in fasting or after a meal The elevation after a meal or a dose of glucose is said to be normal when the peak attained is 0 17 per cent or less and the total duration less than two hours The peak level is said to be less significant than a prolongation of more than two hours

Treatment—We may consider treatment under the following headings

1 *Acidosis*

(*A*) In the early stages before ketosis has resulted in enough depletion of the alkali reserve to cause clinical symptoms (symptoms of acid intoxication)

(*B*) In the intermediate stages in which the depletion of the alkali reserve is enough to cause symptoms of mild or beginning intoxication (p 614)

(*C*) In the more advanced stages with symptoms of deep intoxication pre-coma or coma (p 615)

2 *Surgical and Medical Complications*

3 *General Treatment*

Acidosis—(*A*) Without Symptoms of Intoxication—The presence of aceto acetic acid in the urine implies the presence of an even greater quantity of β hydroxy butyric acid and a continuing drain on the alkali reserve It should be checked at once before it leads to intoxication In checking a ketosis it is desirable to follow a more or less stereotyped orderly plan that a pa tient can learn so that he may apply it him self on future occasions and to use the opportunity for a demonstration The follow ing plan has been proved reliable

Emergency Program —Divide the twenty-four hours into 4 six hour quarters Let the periods begin and end at 6 A M and 12 A M, and 6 P M and 12 P M (or at 7 A M, 1 P M 7 P M 1 A M) At the end of each period empty the bladder test the urine for sugar and acid give a dose of insulin and a *standard feeding* On discovering ketosis *in the absence of symptoms* start the procedure at the beginning of the first regular period thereafter

A *standard feeding* may consist of 400 Gm (2 glasses or a pint) of milk (or 2 parts milk to 1 of cream) or 300 Gm orange juice or equivalent (28 to 30 Gm sugar) The exact quantity is nonessential but it should be the same in each period It is not necessary to provide a maintenance ration

The Initial Insulin Dose —With a patient who has not been taking insulin 5 to 10 units with one who has, a quarter of the regular twenty four hourly dose is given *If the patient has been using protamine insulin* (alone or in combination with regular insulin) it is better not to disturb the protamine insulin The usual dose of protamine insulin may be given daily at the regular hour *in addition to* the doses of regular insulin each six hours In case acid should be discovered for the first time before breakfast the emergency program need not be begun unless acid is still present before the noon meal

The Second Insulin Dose —When at the end of the first period the urine still shows sugar and a positive ferric chloride reaction make the second dose 5 units more than the first

Following Doses —So long as acid persists at the end of a period make the next dose 5 units more than the last When acid is absent but sugar persists make the next dose the same as the one preceding With acid absent and sugar fading make it 5 units less Sugar free urine or an insulin reaction before the end of a period may call for a reduction of more than 5 units When the urine has remained nearly sugar free and the patient free of insulin reactions for two successive periods on the same dose of insulin take steps toward resuming a normal schedule

Discontinuing the Emergency Program —This procedure will vary in different cases depending on the height of the insulin dosage the presence or absence of complication, *etc* *In more difficult* cases the following steps may be taken (1) replace the standard feeding morning noon and evening with *equivalent mixed meals composed of foods* that will appear in the final breakfast, luncheon and dinner (Example orange juice 100 Gm, egg 50 Gm bread 20 Gm. butter 5 Gm and cream 25 Gm, roughly equivalent in C P and F to 400 Gm milk, *may serve as a breakfast substitute* and so on) (2) At midnight drop the standard feeding and give half the calculated insulin dose (3) *Build up the breakfast* luncheon and dinner, meanwhile retaining a dose of insulin before each meal (4) Convert the midnight into a bedtime dose reduce it as fast as conditions permit and adjust and condense the remaining doses

(*B*) WITH SYMPTOMS OR MILD OR BEGINNING INTOXICATION —In the presence of such symptoms (p 614) the treatment may be conducted by six hour periods as in cases with ketosis without toxic symptoms (*A*) but with the following variations

1 Begin treatment at once regardless of hours

2 Omit the feedings until the toxic symptoms disappear

3 Make the first dose of insulin decisive so that symptoms disappear within the first six hours

A decisive dose may be 1 unit per kilogram of body weight Err on the side of giving more than required rather than too little In the presence of symptoms there need be no fear of insulin reactions There should be fear of coma When the symptoms have been stopped including the nausea and the urine obtained at short intervals shows little sugar there may then be danger of a reaction but it is easily preventable by oral doses of 50 to 100 Gm of orange juice hourly or enough to keep sugar passing into the urine Even with vomiting from other causes besides acidosis if a pool of sugar is kept in the stomach enough will usually pass through the pylorus to prevent reactions (*e g* a teaspoonful of 50 to 100 per cent sugar in tea or water every half hour and after each emesis) When symptoms are gone proceed as in (4) In this case also if the patient has been taking

protamine insulin the usual dose can be given daily at the regular hour in addition to the one of regular insulin given at that hour in the emergency schedule

(C) More Advanced Stages —*Precoma Coma*—As in milder cases treatment may be conducted by six hour periods

First Period Management—1 *Give a maximum dose of insulin Establish at once as much insulin action as can be produced by any dose* Two units per kilogram of body weight will probably accomplish as much as more in the first four to five hours but the action curve having reached a peak will have begun to decline by the end of the fifth and be waning definitely in the last hour of the period So in critical cases the dose should be repeated in the middle of the period three hours after the original dose

2 *See that the patient is kept warm* Warm blankets are safest Many patients are burned with hot water bottles

3 *A cleansing enema* to prepare the bowel for the retention of water

4 *A retention enema* of tap water or normal salt solution which may have a volume of 5 cc per kilogram of body weight These cases are always dehydrated by sugar and acid The bowel is an invaluable vehicle for water It should not be dilated by attempts to give too much at once nor irritated by such substances as bicarbonate or sugar Experience has shown that 5 cc per kilogram of warm saline or water will be retained very often once in six hours for a number of periods Attempts to give more may defeat their purpose

5 *Aspirate the stomach contents* to remove possible accumulations of acid and to detect dilatation or atony if present

6 Conditions permitting *give water by mouth* at the rate of 1½ cc per kilogram per hour (about 100 cc or half a glass per 70 Kg) If there is doubt of the motor power of the stomach aspirate after three to four hours and in case of retention allow the stomach to rest and try again later With no retention a more rapid rate may be tried In simple cases it may even be doubled With 1½ cc per hour for six hours by mouth and 5 cc per six hours by bowel the total intake for the period is 14 cc per kilogram or about 1 liter for a patient weighing 70 Kg This rate of water supply continued usually suffices to overcome symptoms of dehydration in two to three periods which is rapid enough for most practical purposes It is not necessary to restore a high normal hydration for the relief of symptoms In extreme dehydration produced by intravenous injections of glucose in dogs the quantity of water required to relieve symptoms may be 3 per cent or less and for full rehydration 5 per cent or less of the body weight There may be no objection to hastening the process of rehydration by giving an extra liter of water in the first period by mouth if conditions permit or otherwise by hypodermoclysis but it is not imperative and extremes are harmful

When the stomach or bowel or both are incompetent part or all of the water must be given parenterally in the form of a normal saline solution by hypodermoclysis For this purpose and especially in later periods the subcutaneous drip at a measured rate is advantageous There is no objection to venoclysis if *slowly* given

7 If the heart needs support caffeine, digitalis or for quick stimulation camphor in oil (repeated at short intervals if necessary) may be recommended

In not too severe cases a fall of the respiration and general improvement may occur in three to five hours from the beginning of treatment but a case would not be severe if symptoms were gone by the end of the period not to mention ketosis and glycosuria In advanced cases therefore insulin reactions are out of the question in the first six hours

Second Period Management—Symptoms continuing even if improvement has already begun it is unsafe to diminish the insulin dosage At the beginning of the period give a maximum dose and maintain the rate of water administration In this period however there will be the possibility of an insulin reaction To avoid this the urine should be obtained at one to two hour intervals (by a retaining catheter if necessary) and examined for sugar and acetoacetic acid With fading ferric chloride and sugar reactions enough sugar should be administered every hour to keep a moderate amount passing into the urine When oral administrations are possible 50 to 100 Gm of orange juice hourly (5 to 10 Gm sugar) will com

monly do otherwise 50 to 100 Gm of 10 per cent aqueous glucose solution hourly by vein or subcutaneous drip When in the middle of the period symptoms and ketosis have disappeared no more insulin need be given until the end of the period If in the middle of the period symptoms persist continue the insulin as in the preceding period If by the end of the period there is no definite improvement of the general condition the prognosis should be guarded *Oliguria* or *anuria* in the first period may be due very largely to dehydration If it persists or appears in the second period, when enough water has been given for urine formation it may be necessary to mobilize water held in the tissues in colloidal union For this purpose 300 cc of 1 4 per cent sodium chloride *solution by bowel (in place of normal saline)* or by stomach tube or intravenously if *necessary* will often suffice If the first dose fails a second may be given More concentrated solutions intravenously given are recommended by some writers (*e g* 50 cc of 10 per cent salt solution) With too concentrated solutions the possibility of thrombosis should be borne in mind There may be some advantage in a supplemental dose of 10 to 15 Gm of sodium bicarbonate given orally or by stomach tube

THE USE OF ALKALI IN COMA —The stopping of abnormal acid production by the administration of adequate doses of insulin stops the depletion of the alkali reserve of the plasma lymph and permits of its rapid restoration by base derived from endogenous sources This restoration begins at once with the fall of the rate of acid production and is usually complete within a short time when acid production has fallen to normal There is thus ordinarily no necessity for the administration of *alkali* for the purpose of restoring the *alkali reserve* so long as the total base reserve suffices for this The administration of an adequate quantity of insulin is the measure of greatest primary importance Next in importance is the restoration of the water balance When the administration of alkali is unnecessary and when it diverts attention from prime essentials or interferes with their execution it should be discouraged *Administrations of alkali by the bowel* are objectionable because they cause irritation of the bowel which renders it useless during the emergency as a channel for the administration of water, and because the quantity of alkali that can be so given is very limited Attempts to give 300 cc of a 3 per cent solution (9 Gm) of sodium bicarbonate in six hours by bowel usually result in nonretention In the presence of a *continuing* acid production even at the moderate rate of 104 Gm in twenty four hours or 26 Gm in six hours the quantity of soda required for neutralization would be 21 Gm per six hour period *Intravenous alkali administrations* are even more objectionable The heart in coma is seriously weakened and may be mechanically overtaxed by the too rapid injection of a large volume of any solution If intravenous injections are made at all they should be given evenly and very *slowly Perhaps 100 cc per hour might* be taken empirically as a limit to be exceeded only with the greatest caution The strength of a bicarbonate solution for intravenous injections should hardly exceed 3 to 5 per cent. With these limitations the quantities of bicarbonate that may safely be given are too small to justify the procedure Thus generally speaking, alkali therapy is non essential and in practice often injurious

But the following facts may be recalled In 1878 Walther published his study of the effects of acid on the animal body which established the principles on which the modern conception of acidosis is founded—that of the alkaline reserve of the blood its existence in the form of bicarbonates the percentage of CO_2 in the blood as a measure of the alkaline reserve etc Walther gave rabbits lethal doses of mineral acids and when symptoms of poisoning had made their appearance gave calculated doses of alkali to some with the result that they promptly recovered while untreated animals died in coma Thus after the administration of a sufficient dose of acid death resulted *even when no more acid was given* but could still have been averted by alkali therapy Before the advent of insulin it was frequently possible when fasting or undernutrition failed to abolish the symptoms of acid intoxication in diabetics by the administration of sufficient quantities of sodium bicarbonate by mouth or stomach tube The quantities given were necessarily large 50 to 100 Gm or more in the course of twelve hours *de*

pending upon the rate of acid production The administration of a sufficient dose of insulin does stop acid production but the action is not instantaneous After the beginning of insulin treatment acid production may be declining but still continuing during a period of six to twelve hours or even longer The effectiveness of insulin is greatly reduced in high acidosis And when treatment has been begun too late patients still die It would appear that when a patient has received a lethal dose of acid death will result even if acid production is stopped The question may be considered as to whether some cases which have or will have received a lethal dose of acid before acid production has been stopped by insulin may not still be saved like Walther s rabbits by alkali treatment that will hasten the restoration of the acid base balance

Management in the Presence of Intercurrent Disease—An intercurrent illness such as a common cold an acute respiratory tract infection a tonsillitis sinusitis or appendicitis an injury a major or minor surgical operation indeed any condition capable of affecting the general health may lower the tolerance of a diabetic or if insulin is used increase the requirement In the presence of any such factor it is therefore desirable to examine the urine at frequent intervals *e g* before or after meals and at bedtime If the condition proves to be innocent nothing more is required If sugar appears when absent before but without acetoacetic acid requisite adjustments may be made If both sugar and acid appear one may proceed as for acidosis without symptoms and continue management by six hour periods as long as conditions may require

Management of Surgical Complications—When the diabetes is under control and an operation is contemplated one may expect that the operation will lower the tolerance or increase the preoperative insulin requirement although with mild enough cases it may not do so When conditions permit it is a good plan to establish a six hour program for three or four periods before the operation and to determine the insulin requirement if any per period on a standard feeding and also fasting for although the postoperative requirement will not be the same it will not be less With cases requiring insulin before operation it is desirable when possible to schedule the operation for the second half of a period so that a standard feeding (or its equivalent in sugar or cereal gruel) may have had time to pass through the pylorus and so that the period may close after the operation The insulin requirement for the first postoperative six hour period may be anything over the preoperative requirement One may start with the latter and closely observe the urine and blood giving an extra dose in the middle of the period if indicated As nausea etc will interfere with feedings the patient may fast or one may administer the usual six hour glucose supply in the form of 5 per cent glucose solution by vein or the subcutaneous drip When prior to the operation the diabetes is already out of control as it may be for example in a case of appendicitis the operation should preferably be deferred until control is established or at least until acidosis is stopped An urgent operation need not be deferred for glycosuria alone as control may be gained in the postoperative periods But acidosis enormously increases risks and can usually be stopped in six to twelve hours

General Treatment—Cure of the disease is beyond reach at present The object of treatment is to maintain life and reduce disability to a minimum—physical mental emotional and economic The patient must be established on a diet that provides the essentials for physical health and gives as much satisfaction as possible Bizarre diets that unduly limit variety are difficult to follow for long periods of time The character and magnitude will necessarily differ with different patients The artisan whose ability to earn his living depends on his physical strength must have food to sustain him or become dependent The scholar artist or musician may do with less From the purely physical standpoint a diabetic does better as a general rule if he is kept spare and a trifle under rather than overnourished

The *education of the patient* is of the utmost importance as it devolves upon him to maintain the advantages gained by an adjustment of his diet insulin etc Systematic education of the patient in all that pertains to the maintenance of the life and health of a diabetic and a systematic follow up service are essential parts of the manage

ment Of vital importance to a diabetic is a knowledge of when to be particularly on the lookout for acidosis, how to detect it and what to do if he finds it as this has to do with the preservation of life

Caloric Requirements—These vary with age sex weight height surface physical activity, state of nutrition and other factors For normal subjects the average requirement may be determined from charts and tables prepared for the purpose such as the following of DuBois and Du Bois and Aub The chart (Fig 60) is based *on the formula* Surface Area (sq cm) = $wt^{0.425} \times ht^{0.725} \times 71.84$

Suppose the patient to be a man thirty five years of age whose weight is 70 Kg and whose height is 170 cm (69 inches) In Figure 60 it will be *found that a horizontal* projection of the point on the height column at 170 cm will meet a perpendicular projection of the 70 Kg point on the base line at approximately 1.8 on the diagonal This means that the surface area of the individual is 1 8 square meters Since Table 1 shows that the hourly caloric requirement of a man between thirty and forty years of age is 39.5 per square meter of surface area this patient will require 1 8 × 39.5 × 24 (hours) or 1730 calories daily under basal or minimal conditions (to maintain his weight)

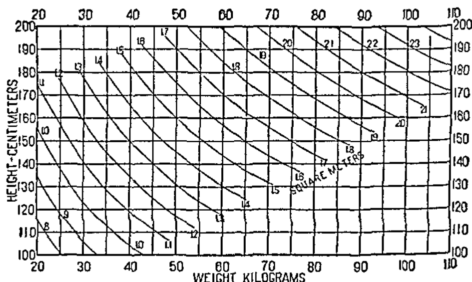


Fig 60—Chart for determining surface area of man in square meters from weight in kilograms (wt) and height in centimeters (ht) according to the formula area (sq cm) = $wt^{0.425} \times ht^{0.725} \times 71.84$ (DuBois)

Having determined the surface area of a patient from the height and weight by means of the chart the average caloric requirement may be read from Table 1

Table 1*—The Average Caloric Requirements per Square Meter of Body Surface in Both Sexes for Different Periods of Life

Age	Calories per square meter per hour Male	Female
14–16	46	43
16–18	43	40
18–20	41	38
20–30	39.5	37
30–40	39.5	36 5
40–50	38.5	36
50–60	37.5	35
60–70	36 5	34
70–80	35 5	33

* Taken from page 122 Aub and DuBois Carnegie Reprint

In actual practice on individual cases a diet composed on the basis of averages may prove to be higher or lower than *required* for the maintenance of a given weight in which case it may be adjusted as requisite *The body weight as observed* over a period of time long enough to avoid confusion resulting from fluctuations of the body content of water is the most practical guide When feasible to do so the plan for maintaining the body weight slightly below the average for normal subjects may be recommended For rapid estimation *of caloric* requirements one may assume that at bed rest 25 calories per kilo are needed at light work 30 at heavy work 35 and upward

PROTEIN REQUIREMENTS —It is possible under suitable conditions to maintain nitrogen equilibrium with quantities of protein as low as or lower than 0 6 Gm per kilo of weight in twenty four hours The tolerance of a patient is often higher or his requirement of insulin lower when the protein intake is kept at a low level However, other factors remaining the same differences observed on diets containing 0.5 and 1 Gm per kilo are seldom significant There is little to be gained and something to be lost by reducing the protein to the lowest possible limits If the protein is between 0 75 and 1.25 Gm per kilo for adults theoretic and practical requirements are met Growing children need 2 to 3 Gm per kilogram

CARBOHYDRATE AND FAT REQUIREMENTS —Having fixed the total and protein calories the balance must be divided between carbohydrate and fat The relative proportions that are most advantageous have been the subject of much discussion In this connection it may be recalled that the effects of given proportions are influenced by the total magnitude of the diet Thus a diet consisting wholly of 100 Gm of fat or carbohydrate would not be high in either component In diets of the type associated with the names of Petren in Sweden and Newburgh and Marsh in this country the preponderance of the nonprotein calories have been made up in fat (as much as 95 per cent in one of Newburgh s diets) On the other hand in the diets employed in the older cures a much higher percentage of the total calories appears in the form of carbohydrate *e g* Donkin s milk cure Mosse s potato cure During s rice cure von Noorden s oatmeal cure The same principle is embodied in the cereal diets of Falta Salamon Porges *et al* and in the high carbohydrate diets employed in this country by Geyelin Sansum Rabinowitch and others In milk containing C 5 P 3 F 4 per cent the C F ratio is 1.25 1 and in human milk 2 1 or higher in skimmed milk 8 or 10 1 In the original von Noorden oatmeal diet the fat sometimes equalled and sometimes exceeded the carbohydrate C F ratios of anywhere from 2 to 8 1 have been used in some of the high carbohydrate diets Diets containing a normal *quantity* of carbohydrates are generally liked by patients better than diets too low in this class of foods But excellent results can be obtained with various types of diet

Procedure in Establishing Diets—The choice of procedures is made on the basis of one s estimate of the severity of the case In relatively mild cases a diet designed for permanent use may be given at once and the results observed for a day or two If the sugar in the urine does not subside promptly one may hasten the process either by giving a lower diet or by using a small dose of insulin before each meal and increasing as requisite With severe glycosuria it may be well to begin with a maintenance diet In cases with heavy glycosuria the writer often begins with the emergency program described above for 2 reasons (*a*) to educate the patient in the use of the method against future needs and (*b*) to insure desugarization within twenty four hours

Insulin and Its Use—INSULIN AS A PROTEIN—The ordinary market preparations referred to as regular or 'standard insulin are purified extracts of the hydrochloride Since Abel s separation of insulin in crystalline form and Sahyun s development of a commercial method *crystalline zinc insulin* has become available on the market and bids fair to replace the hydrochloride extracts The injection of 10 to 20 units of the hydrochloride or of the crystalline zinc insulin results in an action which reaches its peak in three to four hours begins to decline in the fifth hour and has a total duration of eight to ten hours (in average conditions) With the use of such preparations alone any patient requiring more than 20 to 30 units per day will usually have to be given repeated doses To eliminate the disadvantage of multiple doses various methods have been adopted to retard the absorption or liberation of insulin by combining it with other substances such as oil cholesterol protamine histone globin arginine and others The most widely used are preparations of protamine zinc insulin The effects of standard preparations are slow in onset and relatively weak until reinforced by repeated overlapping doses but slow to disappear A single dose of 20 units of protamine insulin may have an action lasting 30 hours But after patients have received large doses daily for days or weeks effects

may be observed for several days after discontinuance The effects of a single moderate dose begin slowly, rise gradually attain a maximum between eight and twelve hours later and then gradually decline So if a single dose is given before breakfast the greatest effect is commonly between 4 and 8 P M The ideal curve would be one rising rapidly enough to cover breakfast lunch and dinner and falling rapidly enough to avoid insulin reactions between bedtime and breakfast without the necessity of a bedtime feeding Various attempts have been made to accomplish such curves Some dozens of combinations have been described Graham, Wilder and associates Colwell and associates have had considerable success with mixtures of protamine and hydrochloride or zinc crystalline insulin In cases requiring more than a limited dose per day one may use either separate doses of protamine and free insulin or such a mixture The mixture of three parts of standard or crystalline to one of protamine insulin recommended by Colwell, Izzo and Stryker has been used increasingly in the writer s clinic in the course of the past year For a full discussion of this subject with accurately plotted action curves see Colwell *et al* (Ref)

The method of administration favored in the writer s clinic a year ago was that of giving as much protamine insulin before breakfast as might be required to keep the urine sugar free or nearly so in the fasting quarter between midnight and morning (but not enough to cause insulin reactions in that period) If that quantity of protamine insulin given in the morning failed to control glycosuria by day as would be the case especially after breakfast and to a lesser extent after dinner at night in more advanced cases it was supplemented by a dose of regular insulin before breakfast and occasionally by a small dose of regular insulin before the evening meal although the latter was usually not required With patients adjusted on such a regime it was often found that the ratio of protamine to regular insulin was between 2 and 3 1 Latterly, as stated, we have tended to use single A M doses of 3 1 mixtures in many cases

For the handling of emergencies the quicker acting regular (or crystalline zinc) insulin is superior to protamine insulin (or equivalent) and it is better to avoid the possible confusion that may result from using the two together The full effects resulting from a change of the dose of protamine insulin will not be registered within twenty four hours whereas the full effect of a dose of regular insulin is obtained within ten to twelve hours so that in rapidly changing conditions it is preferable to use the more adjustable form

Hypoglycemic Reactions—Insulin Reactions—The commonest symptoms of a mild reactions are those felt with great hunger, weakness faintness pallor, tremor nervousness sweating those of more marked reactions—emotional symptoms laughing crying excitement, fright diplopia confusion disorientation or amnesia of severe reactions—muscular spasm and narcolepsy The pulse is commonly elevated and in the unconscious state the pupils are dilated In exceptional cases mono or hemiplegias appear and clear with the passing of the other manifestations Delay in recovery has been observed for days or months In uncomplicated cases death very rarely, if ever occurs The blood sugar percentage during a reaction may range from 0 09 downward to 0 02 or lower The degree of the depression varies in different cases and there is no exact correspondence with the symptomatology This is due partly to varying relations between the blood sugar concentration and the total body content of glucose and partly no doubt to other factors The time of a reaction is most commonly three to four hours after a dose of regular insulin followed by a meal as the action of insulin continues in the postabsorptive period Thus after a morning dose and breakfast a reaction may occur between 10 and 12 A M or 1 P M., and after an evening dose and dinner, between 9 and 12 P M After a large morning dose sufficiently covered by breakfast and lunch a reaction may occur in the late afternoon between 3 and 6 They are rarely belated more than eight hours with regular insulin After a dose not followed by food a reaction is possible within an hour After protamine insulin a dose given in the morning may cause a reaction in the afternoon or after midnight or before breakfast the following day Such reactions are apt to develop more slowly and when stopped may

recur in an hour or two Exercise or exertion may hasten or determine an insulin reaction by increasing the total consumption of sugar and the quantity burned per unit of insulin Mild insulin reactions disappear quickly after the ingestion of sugar orange juice or equivalents *With severe reactions in which the patient is not sufficiently conscious to swallow voluntarily attempts to administer fluids by mouth are best avoided for fear of aspiration and possible pneumonia* The subcutaneous injection of adrenalin hydrochloride 1 1000 (obtainable in ampules of 1 cc) will often restore consciousness within a few moments and may then be followed by sugar or orange juice given by mouth The dose of adrenalin may be for a child 0.3 to 0.5 cc for an adult 0.5 to 1 cc Its effectiveness depends on the mobilization of glucose from glycogen Cases in which the latter is too greatly depleted require intravenous injections of glucose

Spontaneous hypoglycemic symptoms appear in some cases of diabetes when no insulin has been given See section on Spontaneous Hypoglycemia

ROLLIN T WOODYATT

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SPONTANEOUS HYPOGLYCEMIA

Definition—The term spontaneous hypoglycemia is here used in the purely descriptive sense to denote clinical pictures distinguished by symptoms of hypoglycemia and low normal or subnormal blood sugar levels The classification includes cases in which the hypoglycemia is due to excessive insulin production (*hyperinsulinism*) and others that arise from other causes

History.—The discovery of insulin (1921-22) led directly to knowledge of the symptoms that may accompany hypoglycemia The spontaneous occurrence of similar symptoms in 5 clinical cases in association with hypoglycemia was reported by Harris in January 1924 Harris considered the hypoglycemia to be due to excessive insulin secretion and in a series of papers developed the conception of *hyperinsulinism* as a disease entity as definite as the opposite condition *hypoinsulinism* or diabetes In 1927 Wilder and associates reported a case in which exploration revealed a metastasizing islet-cell carcinoma and in which insulin was recovered from the tumor tissue A few months later Finney and Finney explored a case in which the pancreas presented a normal appearance and in which partial resection was without definite benefit. In 1930-1931 Derick, Carr Evarts Graham and associates reported cases with islet-cell adenomas that were successfully removed with cure of the symptoms In the fall of 1934 there were reported in the literature 19 laparotomized cases All of these reports were by American authors In the meantime some hundreds of unexplored cases with varying degrees of hypoglycemia and a great diversity of symptoms were reported or cited here and abroad as cases of *hyperinsulinism*. The term *dysinsulinism* was proposed by Harris to describe cases exhibiting both hyperglycemia and hypoglycemia at different times

Etiology—The etiology may differ in different cases In a large proportion we are dealing with inborn defects of the sympathetic autonomic endocrine system of the same general order as those involved in other constitutional diseases of unknown cau e (diabetes migraine peptic ulcer gout and so on) In cases of true hyperinsulinism that happen to be associated with islet adenomas or carcinomas the etiology is no clearer than that of new growths in other parts Of other cases associated with hepatic dysfunction a fraction are due to acquired diseases (intoxications infections affecting the liver) but the majority as

stated are inborn defects *Excessive or unusual intakes of food and especially sweets* have often preceded the onset of symptoms These and *fatigue* are commonly recognized as provocative factors

Morbid Anatomy —To the end of September, 1939, there were reports in the literature of 62 cases that had been surgically explored or examined postmortem Islet cell tumors were found in 23 hypertrophy of the islets in 5, pancreatitis or unknown pathology in 3 The pancreas was normal in 31 A large proportion of the tumors were adenomas Some having the appearance of carcinoma on histologic examination have been encapsulated and nonrecurrent A minority were proved to be carcinomas Among the 200 cases of the milder types reported by Cammidge there was evidence of organic disease of the liver or hepatic dysfunction in a considerable number Harris refers to pancreatitis in association with gallstones or peptic ulcer

Lesions reported by various writers to November, 1940, are indicated in the following tabulation by Conn (For literature references see original)

I Organic—recognizable anatomic lesion
- (a) Hyperinsulinism
  1. Pancreatic island cell carcinoma
  2. Pancreatic island cell adenoma
  3. Generalized hypertrophy and hyperplasia of islands of Langerhans
- (b) Hepatic disease
  1. Ascending infectious cholangiolitis
  2. Toxic hepatitis
  3. Diffuse carcinomatosis
  4. Fatty degeneration "Fatty metamorphosis"
  5. Glycogenosis (von Gierke's disease)
- (c) Pituitary hypofunction (anterior lobe)
  1. Destructive lesions (chromophobe tumors cysts and so on)
  2. Atrophy and degeneration (Simmonds disease)
  3. Thyroid hypofunction (secondary to pituitary hypofunction?)
- (d) Adrenal hypofunction (cortex)
  1. Idiopathic cortical atrophy
  2. Destructive infectious granulomas
  3. *Destructive neoplasms*
- (e) Central nervous system lesions (lesions of brain and brain stem said to interfere with nervous control of blood sugar)

II Functional—no recognized anatomic lesion
- (a) Hyperinsulinism (autonomic nervous system imbalance?)
- (b) Renal glycosuria (severe degrees of low renal threshold for dextrose)
- (c) Severe continuous muscular work
- (d) Pregnancy and lactation

Physiology —The maintenance of normal blood sugar levels depends on the balance of many factors The influence of any single factor is necessarily relative to that of others Whereas, all other factors remaining the same, a rise or fall of insulin secretion may account for a hypoglycemia or hyperglycemia it does not follow that in pathologic conditions all other factors *are* the same Hypoglycemia can be produced in animals by the administration of insulin But it can also be produced in the absence of insulin by hepatectomy (Mann), hypophysectomy (Houssay), or adrenalectomy (Long and Lukens) So in the interpretation of hyperglycemias or hypoglycemias observed in the clinic it is necessary to consider other factors besides insulin secretion The power of the body to maintain normal blood sugar levels depends to a large extent on the liver Whereas the blood sugar regulating function of the liver is affected by elements (hormones etc) from other organs the liver itself is essential for blood sugar regulation In cases of spontaneous hypoglycemia with islet hypertrophy or islet tumors it might seem not improbable that we are dealing with actual *hyperinsulinism* In the milder cases it is necessary to consider other factors Those cases that exhibit quick oscillations from hyperglycemia to hypoglycemia referred to as cases of *dysinsulinism* and which might better be described as *poikiloglycemia* suggest disorders of the blood sugar *regulating* mechanism.

Symptoms —Those of insulinogenic hypoglycemia are discussed in the chapter on diabetes Harris distinguishes the following types

Mild Type —With spells of hunger weakness anxiety pallor especially about the lips sweating and trembling These spells occur at night or before breakfast luncheon or dinner or when the stomach is empty They disappear in a few minutes after the ingestion of sugar

Moderately Severe Type —With profuse sweating prostration more marked anxiety mental lapses periods of unconsciousness and spasms of isolated groups of muscles Attacks of this type may closely resemble *petit mal* but they are always relieved by the ingestion of sugar

Severe Type —With recurring attacks of

unconsciousness convulsion narcolepsy, associated perhaps with major hysteria or actual psychosis these attacks may resemble *grand mal* epileptic seizures

Abdominal Pain—Cramplike abdominal pain had led to cholecystectomy and appendectomy in cases of pancreatic adenoma described by Evarts Graham and others Harris speaks of 3 cases with pain in the midportion and upper left quadrant The pain disappears with relief of hypoglycemia Occurring at times when the stomach is empty and being relieved by food it is easily confused with gastric or duodenal ulcer

In the milder cases the clinical course is extremely variable In the more severe cases it may be rapidly progressive To control the symptoms it may be necessary to give feedings at intervals as frequent as every two hours The frequent feedings and interruptions of sleep may eventually lead to nonretention of food and require the use of parenteral injections Failure to control the hypoglycemia may result in death

Diagnosis—The diagnosis of hypoglycemia rests on the clinical history of recurring attacks coming on at hours of the day when the stomach is empty and relieved by the administration of sugar The demonstration of hypoglycemia confirms the diagnosis However when symptoms are not relieved by the ingestion of sugar even though the blood sugar is below the norm the question arises as to whether the low blood sugar level is actually responsible for the symptoms or not In cases of true hyperinsulinism relief from the ingestion of carbohydrate is definite and constant

'One fasting blood sugar determination or one glucose tolerance test is not always sufficient because there seem to be periods when the patient with hyperinsulinism will show normal readings The element of mental and physical fatigue affects blood sugar levels and in making tests the ambulatory patient should not be permitted to lie down The glucose tolerance test should be carried out for six full hours because in some cases the blood sugar levels may remain normal for the first four hours and fall to very low levels in the fifth and sixth hours (Harris) It has been shown by Conn that a patient on a low carbohydrate diet may fail to show a characteristic blood sugar curve but does so on a high carbohydrate diet and proposes the use of a standard high carbohydrate diet in preparation for a tolerance test

The characteristic blood sugar curve shows an unusually low or a normal peak and subsequent depression below that observed in normal cases

Treatment—In the course of attacks the treatment is that of insulin reactions (p 624) It should be noted however that the administration of sugar is very prone to be followed by even greater depressions of the blood sugar level than existed before and may lead to the production of further attacks In cases that have been sufficiently mild to permit Waters Sweeney Harris and others have reported favorable results from the use of low carbohydrate high fat diets The diets described have contained approximately 1.25 to 2 Gm C 2 to 2.3 Gm F and 1 Gm P per kilo per day (or about 20 to 140 Gm C 70 Gm P and 140 to 160 Gm F for the average patient) These diets are divided in 5 to 8 feedings But in the more severe cases it is impossible to adhere to diets of this type and more sugar must be given to prevent convulsions In certain mild cases the author has observed beneficial results from the use of injections of APL or insufflations of powdered anterior lobe (1 Gr t i d) Ephedrine is at best but mildly effective Epinephrine (1 mg b i d) may prevent attacks in milder cases Theoretically a diabetogenic extract of the anterior pituitary or of the adrenal cortex (Compound E Kendall) should be effective but available preparations of the adrenal cortex or anterior lobe that are sufficiently pure for clinical use have little diabetogenic effect In cases with severe recurring attacks it is necessary to institute frequent feedings at whatever intervals may be required In very severe cases the amount and number of feedings required to avoid convulsions may be more than the patient can take and retain and it is then necessary to use subcutaneous or intravenous glucose injections

In the more severe cases surgical measures must be considered When the exploration reveals a pancreatic tumor it should be removed When the pancreas appears normal partial resections have failed to give satisfactory results Subtotal resection as first

done by Graham, has resulted in cure in a number of cases In 1940 the literature contained reports of 10 cases subjected to subtotal resection of which 5 were cured, 2 improved and 3 unimproved In 3 of the cases there was islet hypertrophy while the pancreas was normal in the other 7 Of 17 cases in which tumors were removed 8 were cured 1 improved 3 not improved and 5 died as the result of the operation Many more had been reported at the end of 1942 In those cases that are associated with surgical conditions of the liver gallbladder or biliary tract relief of those conditions may result in improvement of the hypoglycemia

ROLLIN T WOODYATT

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DIABETES INSIPIDUS

Definition—*Diabetes insipidus* is a chronic disease characterized by the passage of a large amount of very dilute but otherwise normal urine and by an enormous thirst

Incidence—It is a relatively rare condition which chiefly affects young people and is seen in males more frequently than in females The importance of heredity has been well illustrated by the study of a number of interesting families one of which (reported by Weil) included twenty three victims of persistent polyuria among the ninety one members of four generations

Symptoms—There are two general groups of cases (1) the so called *primary* or *idiopathic* in which no organic disease is demonstrable and (2) the *secondary* or *symptomatic* which is associated with an organic lesion of the brain or other parts. The lesions mainly associated with this second type are those produced by fracture of the base of the skull and other cranial injuries, basilar meningitis especially of syphilitic origin tumors of the brain particularly those of the hypophysis and neighboring structures cerebral hemorrhage encephalitis etc There are also reports of its association with tumors and aneurysms within the abdomen and with tuberculous peritonitis In cases of the *primary type* there may be no symptoms except those of the *diabetes insipidus* and at autopsy no characteristic gross lesions except perhaps some enlargement and congestion of the kidneys dilatation of the ureters, and hypertrophy of the bladder In the secondary type the symptoms may be numerous and are those characteristic of the associated lesion

The disease which may be congenital may begin suddenly after an injury, after an emotional shock or after an infectious disease Usually the onset is insidious with gradually increasing polydipsia and polyuria Trousseau's famous patient secreted 43 liters of urine in twenty four hours and drank a corresponding quantity of fluid It is said that one child passed a quantity of urine in one day the weight of which almost equalled that of the boy himself Usual quantities vary from 8 to 12 liters in twenty four hours The *urine* is quite pale, almost colorless of low specific gravity (1 001-1 005) and contains as a rule no abnormal elements The *thirst* is sometimes insatiable or the satisfaction of it may be the greatest pleasure of life When deprived of water the patients may suffer extremely and under such circumstances they have been known to drink their own urine It is easy to imagine the deleterious effects especially on a nervous person of the inconvenience the embarrassment the interference with daily activities but particularly of the insomnia so often produced by the frequent necessity of arising at night to allay the thirst and to pass urine Nevertheless in some cases the general health is satisfactorily maintained

and patients may live with the disease for fifty years The course of the secondary form of the disease depends upon that of the associated lesion and as might be expected the general health often fails rapidly

With the marked polyuria there are evidences of a lack of fluid elsewhere in the body the quantity of saliva is decreased, the skin is dry there is no sweating and constipation develops While the concentration of the urine is very low a normal amount of solids is passed in twenty four hours Increase of the nitrogenous food intake leads to increased output of nitrogen in the urine and an increase of the chlorides in the diet also increases the quantity excreted but with a great aggravation of the polyuria When the fluid intake is restricted the specific gravity of the urine rises somewhat and the amount of urine diminishes but not to normal In most cases after the hypodermic injection of pituitrin the polydipsia and polyuria practically disappear the concentration of the urine becomes normal and all renal functional tests are normal No significant metabolic disturbances have been demonstrated other than that of the water balance and the delicate adjustment in the blood between solids and fluids and in the amount of dissolved substances is maintained as steadily as in health

Pathogenesis —The current status of this complex and intriguing problem may be briefly summarized as follows

Experimental and pathologic studies indicate that diabetes insipidus may be caused by a disturbance of the posterior lobe of the pituitary gland by a lesion involving certain nerve centers in the hypothalamic region or by the interruption of the nerve tracts that pass between the nerve centers and the posterior lobe of the pituitary Lesions of the pituitary stalk are particularly prone to be followed by this syndrome The removal of the entire pituitary gland may cause a temporary polyuria and polydipsia and Richter insists upon the importance of a persistent and functioning anterior lobe

The relative importance of hormonal influences is suggested by several observations namely (1) the experimental condition may be induced in animals whose kidneys have been denervated (2) the antidiuretic principle of posterior pituitary products is effective in the complete absence of autonomic nervous influences, (3) the experimental disease may be transmitted by the blood to another animal by cross circulation experiments and (4) the remarkable observation of Mahoney and Sheehan that the extreme polyuria and polydipsia produced in dogs by the occlusion of the pituitary stalk with a silver clip can be abolished by subsequent total thyroidectomy and reestablished by oral administration of de iccated whole thyroid gland Alternate states of extreme polyuria and oliguria could be produced at will

Diagnosis —*Diabetes insipidus* is usually easily distinguished from *diabetes mellitus* by the glycosuria and the high specific gravity of the urine during the latter disease Rarely the two conditions are coexistent

Hysteric polyuria may simulate *diabetes insipidus* This primary polydipsia is in most instances transitory and there are usually other evidences of hysteria

A large amount of urine of low specific gravity may be passed by some patients with chronic nephritis but the presence of albumin and casts in the urine the arterial hypertension and the results of renal function tests should make the diagnosis easy

Treatment —Treatment should be based upon a thorough study of each case Syphilitic cases should of course receive antisyphilitic therapy Cures have been reported following simple lumbar puncture following x ray therapy to the pituitary region and after the administration of the anterior pituitary like hormone that is contained in the urine of pregnant women

Usually cures are not obtained but symptomatic measures may be most helpful No attempt should be made to reduce the amount of liquid The diet should contain only the minimal requirement of salt but otherwise need not be restricted Of the many drugs that have been tried amidopyrine is occasionally helpful and may be given in 1 Gm doses at noon and at bed time

Products of the posterior lobe of the pituitary gland are of great value After a sufficient dose the thirst disappears and the concentration and the quantity of urine become comparatively normal As a general rule it is most effective when administered

subcutaneously two to four times a day A trial may be made of the intranasal application of pituitary products A liquid may be used as a spray or on pledgets of cotton placed high in the nasopharynx Recently it is said that a more effective method has been found in the use of snuff of posterior lobe powder When this last named method is effective the administration becomes quite simple and the cost is greatly reduced

T P SPRUNT

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LIPOMATOSIS

Definition—Various observers have described a number of different types of localized or unusual deposition of fat all of which may be grouped under the term lipomatosis' to distinguish them from the ordinary form of obesity Lyon has pointed out the transitions between types and considers them not clinical entities but variations of a common morbid process

Clinical Types—(1) *Nodular Circumscribed Lipomatosis*—Single or multiple encapsulated lipomata are very common vary greatly in size and affect women more frequently than men They are soft and lobulated as a rule and although they usually cause no symptoms may be tender or even spontaneously painful When very numerous or very unfortunately situated they may cause mechanical interference with normal functions

(2) *Diffuse Symmetric Lipomatosis* (FETTHALS, ADENOLIPOMATOSIS—In diffuse symmetric lipomatosis the fatty masses are not encapsulated, they are more common in men than in women may be of very large size, and very disfiguring The term 'fat neck appropriately indicates the marked predilection for this region Huge masses may cover the shoulders and extend down the arms or may be arranged in segmental fashion on the thorax Sometimes there is a remarkable localization in regions rich in lymph glands so that at first sight a disease of these structures is suggested Lymphoid tissue or hemolymph nodes may be found in the masses but are no more characteristic of this type than of the other forms of lipomatosis Although symptoms are usually absent those more characteristic of Dercum s syndrome may be present

(3) *Adiposis Dolorosa* (DERCUM S DISEASE)—The cardinal features of *adiposis dolorosa* are fat deposits pain asthenia and psychic manifestations The condition is much more common in women than in men and is apt to occur in fat neuropathic individuals at the time of the menopause Spontaneously painful very tender irregular deposits may appear in the subcutaneous fatty tissues On palpation they may resemble a caking breast or feel as though filled with a bundle of worms' Asthenia is usually a striking feature Rheumatic pains appear in muscles and joints The onset is insidious Exacerbations and remissions occur, but the symptoms usually persist to some extent

(4) *Adipositas Cerebralis*—Under the heading of *adipositas cerebralis* may be grouped all disturbances due to intracranial lesions or associated with a deficient functioning of the hypophysis The *dystrophia adiposo genitalis* of Frohlich (1901) is the classic example The symptoms of such cases with a gross lesion usually a tumor of the hypophysis or neighboring structures may be

(a) Due to the brain tumor
   (1) General symptoms of increased intracranial pressure headache vomiting etc
   (2) Neighborhood symptoms due to local pressure visual disturbances hemianopsia optic atrophy changes in the sella turcica

(b) Referable to the loss of hypophyseal function (?), adiposity genital dystrophy, perhaps polyuria, and so on

(5) *The Lipomatosis of the Pseudohypertrophic Form of Muscular Dystrophy*—In lipomatosis of the pseudohypertrophic form of muscular dystrophy the dystrophic muscle groups may be strikingly enlarged by marked infiltration of adipose tissue between the muscle bundles There may also be unusual fatty deposits in the mammary and inguinal regions

(6) *Lipodystrophia progressiva* a rare condition in its fully developed form begins in childhood and affects girls almost exclusively It is characterized by a sadly disfiguring emaciation of the upper portion of the body with a remarkably complete disappearance of subcutaneous fat and by a grotesque obesity of the lower half of the body The general health may be good but there are often psychoneurotic symptoms

Morbid Anatomy—At autopsy in cases of lipomatosis the associated lesions of other structures especially of the endocrine glands are of considerable interest but the variety of the lesions even in cases belonging to the same clinical group prevents any clear understanding of the relationship Even in *dystrophia adiposogenitalis* different structures have been affected and some disturbances have been attributed to primary gonadal changes In Dercum s disease pituitary tumors have been found as well as thyroid changes Marine believes that atrophy of the thyroid is the characteristic lesion Degenerative changes in the peripheral nerves have been noted and may account for some of the symptoms

It is universally recognized that these fatty peculiarities are of endogenous origin but there is question as to whether they are due to disturbances in hormones (internal secretions), to changes in the nervous stimuli or depend upon powers inherent in the cells of the subcutaneous tissue Each theory has its advocates and it may be that all three are in some way combined

Treatment, except when the fatty masses may be removed by operation is unsatisfactory Small doses of dried *thyroid* or of *thymoxin* may be of value in *adiposis dolorosa* and whenever the metabolic rate is retarded *Pituitary extracts* may be tried in appropriate cases *Leptynol* is a German preparation of palladium in lanolin for local injection into fatty masses The *dietetic hygienic regimen* should be adapted to the state of general nutrition

T P SPRUNT

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HEMOCHROMATOSIS

Definition—*Hemochromatosis* or *bronze diabetes* is a disease of metabolism characterized by a marked *deposition of pigments* especially the iron containing hemosiderin in many organs of the body by *cirrhosis* particularly of the liver and pancreas and in most cases by *diabetes*

Incidence—Sheldon has collected 311 cases of which thirteen were in women The disease usually appears in middle aged men but though symptoms begin at this time of life it is evident that the pathologic process originates many years earlier

Etiology—The cause of hemochromatosis is not understood There is difference of opinion concerning the relationship of the pigmentation and of the cirrhosis to each other There is a marked disturbance of the intracellular iron metabolism although that of the hemoglobin seems to escape entirely There is a marked retention of iron in the body as much as 40 Gm or ten times the normal amount and as it seems from metabolism experiments that the retention is not complete many years must be required for its accumulation The chemical analyses of organs indicate some retention also of copper sulfur and calcium The possibility of copper poisoning in the etiology of hemochromatosis has been stressed by Mallory and others but recent work does not tend to support it The diabetes is generally attributed to the pancreatic lesion but the wide involvement of the endocrine glands is of possible importance in this connection

Morbid Anatomy—At autopsy the en

larged, cirrhotic liver, the pancreas, and the lymph nodes draining these organs are of a striking ochre color Other glandular organs show relatively slight macroscopic pigmentation Histologically hemosiderin is found in large amounts in the liver, pancreas and lymph nodes, and in smaller amounts in the other important glandular structures as well as in the spleen the heart muscle and, in some cases in the capillary endothelial cells of the skin and of the genito urinary tract Hemofuscin a finely divided, light yellow pigment, which does not contain iron, may be found in connective tissue and smooth muscle cells Physiologic pigments are increased

Symptoms—The early symptoms may be those of diabetes In other cases the *onset* is insidious, with asthenia and malaise, or sometimes a complication, such as tuberculous peritonitis, may be the first manifestation

The *skin pigmentation* in well marked instances has a distinct bronze shade and in extreme cases may be even bluish black The mucous membranes are usually not pigmented The *liver* is enlarged and may be tender The *spleen* is usually palpable and firm There is no *jaundice* and no characteristic change in the blood beyond the *slight secondary anemia* so frequent in chronic disease The endocrine involvement may be manifested clinically Genital hypoplasia is fairly frequent The diabetes is usually severe

Diagnosis—A diagnosis of hemochromatosis is suggested by the association of asthenia malaise skin pigmentation enlargement of the liver, and palpability of the spleen, with or without diabetes It may be confirmed by the finding of hemosiderin in the urinary sediment or in a section of excised skin but negative results of these tests are not conclusive

Prognosis—The prognosis is unfavorable After symptoms appear the disease lasts only a few months or at best a few years About 50 per cent of the reported cases have died in diabetic coma The duration of the symptomatic stage has been lengthened since the advent of insulin

Treatment must be symptomatic since our knowledge does not permit rational etiologic therapy The diabetes should be treated like the ordinary type of *diabetes mellitus* About 70 per cent of the cases respond favorably to insulin Some cases are hypersensitive, a few are resistant, to insulin

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OCHRONOSIS

Definition—Ochronosis is a rare metabolic pigmentary disorder which results in darkening of the cartilages and certain of the fibrous tissues and in pigmentation of the skin Degenerative cartilaginous changes may develop into arthropathies

Incidence—There have been reported between forty and fifty cases which may be divided into three groups (1) those associated with alcaptonuria a constitutional familial anomaly of the metabolism of the aromatic amino acids which is manifested by the excretion in the urine of homogentisic acid normally an intermediary product of amino acid catabolism Such urine turns brown on standing or after the addition of alkali (2) Those associated with the prolonged use of carbolic acid applications (3) A smaller group in some of which melanin instead of homogentisic acid may be found in the urine Ochronosis is more frequent in men than in women and usually affects older people

Morbid Anatomy—The most heavily pigmented structures the cartilages of the ears trachea bronchi ribs intervertebral disks and symphysis are dark gray or black Those most involved become degenerated and worn and there is new bone formation (osteo arthritis) The pigment is apparently a melanin and appears microscopically as finely divided yellowish brown granules or else colors the tissue diffusely

Etiology—The etiology of the disturbance is not thoroughly understood but in all cases there is doubtless a large constitutional (probably inherited) factor Most alcaptonurics do not show ochronosis and consequently the causes of the two conditions cannot be exactly the same It is generally believed that melanin is formed from proteins through the aromatic amino acids probably through the activity of tyrosinase

Symptoms.—There may be no symptoms The earliest manifestations consist of a bluish coloration of the ear cartilages black flecks or streaks in the sclerae the slight pigmentation of the skin of the face In advanced cases there is marked skin pigmentation discoloration of the tendons of hands and feet greenish brown axillary sebum a brownish black cerumen and usually an osteo arthritis especially of the larger joints The urine of course should be carefully examined

Treatment—Careful search should be made for any possible extrinsic cause such as the use of carbolic acid or exposure to similar chemicals Attempts may be made to reduce the exogenous protein component by reducing the dietary protein to the minimum 0 7 to 0.8 Gm per kilogram of body weight and selecting proteins of low tyrosine and phenylalanine content The joint symptoms may be treated as in other types of osteo arthritis

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OBESITY

Definition—Obesity is a state in which the amount of fat stored in the body is excessive

Incidence—Obesity is one of the commonest ailments to which the flesh is heir and is of importance to the individual in proportion to its degree and its association with other diseases To the community it is of importance in that it may *per se* decrease human efficiency and shorten human life The latter is proved conclusively by the data of life insurance companies

Etiology—The fundamental cause of obesity is a positive energy balance That is the caloric value of food absorbed is greater than the total expenditure of energy A comparatively slight disproportion between fuel intake and combustion may over a period of years result in a marked grade of obesity Indeed the extraordinary thing is not that so many persons become obese but rather that more do not Most persons preserve a constant and normal weight in spite of marked variations in their bodily activity and without conscious regulation of their food intake This is because the normal appetite ordinarily adjusts intake so accurately that it just meets but does not exceed the requirements of energy expenditure When this adjustment loses its delicacy and eating falls under the rule of habit obesity may develop Rationing will probably reduce the incidence of obesity

Morbid Physiology—Obesity may be divided into two main types sometimes called exogenous and endogenous In the exogenous variety the acquisition of excess weight coincides with either an increased ingestion of food or a decrease in bodily activity or both the fundamental rate of oxidation in the body remaining unchanged In the endogenous type the explanation of the weight gain is traceable to a drop in fundamental rate of oxidation in the body due to a disturbance in the function of one or more of the endocrine glands It is important to note that in either type the excess storage of fat is due to a simple disproportion between the intake of food and the energy requirement of the body The endogenous cases are endogenous merely in the sense that in the creation of such a disproportion a fall in the rate of oxidation in the body

plays a role Coming in this category may be mentioned obesity associated with hypothyroidism, with hypopituitarism (Frohlich s syndrome of *dystrophia adiposogenitalis* also Dercum s disease and Cushing s syndrome) and with dystrophies of the gonads A much greater proportion of obese persons belongs to the exogenous group

That no fundamental alteration in rate of combustion exists in simple or exogenous obesity is amply proved by studies of the so called 'basal metabolic rate For example by the DuBois standards a series of 41 obese persons studied at the Massachusetts General Hospital showed an average variation from the expected metabolism of but 0.5 per cent Similar results have been obtained by others

Nevertheless it is a matter of common belief that certain persons tend to gain weight while others *apparently* eating as much and exercising no more do not The explanation of this is not to be found in the kind of food ingested The ratio between total calory intake and total calory output is what counts All excess calories after the glycogen depots are filled are stored in the body in the form of fat whether they were originally derived from fat protein carbohydrate or alcohol Differences in energy reaction to similar stimuli may explain some of the differences in the tendency to gain weight While the basal metabolic rate of an individual who gains weight readily may be the same as that of one who does not their total metabolisms may be different and it is the total metabolism in relation to fuel intake which determines weight behavior The performance of muscular work and the ingestion of food accelerate metabolism so do emotional disturbances probably through the liberation of adrenalin Total metabolism consists in basal metabolism plus the increments due to all these causes It is entirely possible that the individual who gains weight readily reacts less intensively to such stimuli than one who has no such tendency In the former the total metabolism would be less than in the latter even though the basal rate of the two were the same

For the most part clinical experience bears out such an hypothesis Individuals who gain weight readily even though they apparently do not eat to excess are usually phlegmatic, they worry less, sleep either longer or more soundly and when at rest relax more completely than persons of the normal or thin types

Morbid Anatomy—In the milder grades of obesity there is simply an excess of fat in the normal fat depots such as the subcutaneous and retroperitoneal tissues, the breasts and the omentum In the severer grades fat infiltration is found also in parenchymatous organs such as the heart and liver

Symptoms—Slight degrees of obesity cause no symptoms As adiposity increases, the extra weight of itself gives rise to a certain amount of dyspnea on exertion and perhaps to increased tendency to fatigue When the obesity becomes extreme the state of corpulence alone may lead to mechanical limitations finally ending in nearly complete incapacity The symptomatology of obesity is however most conspicuously of an indirect variety The added burden of fat puts the whole body under the strain of extra work which manifests itself in an exaggeration of the symptoms due to any coexisting morbid tendency As a recent writer has well put it fat is a parasite The patient suffers chiefly from the effect of his obesity upon his other bodily weaknesses Thus the cardiac patient who becomes obese is in increased danger of cardiac failure and the kidneys pancreas and liver of the obese carry an abnormal load It is generally conceded that obesity predisposes to diabetes and it is also true that often the obese have moderate arterial hypertension which tends to decrease when their weight is reduced

Diagnosis—Inspection gives the diagnosis The determination of cause is the important thing The habits of eating and exercise should be investigated and an attempt made to discover whether the cause lies in excessive food intake insufficient exercise or both Upon such an evaluation will depend the success of treatment The existence of endocrine factors must also be determined Metabolism studies aid in the recognition of these In the thyrogenous obesity the basal metabolic rate is invariably decreased

Prognosis—The prognosis depends upon the grade of obesity and the willingness of the patient to reduce Acute infections par-

ticularly pneumonia also cardiac and renal lesions are more serious in the obese particularly in the very obese than in otherwise normal persons

Treatment —Prophylaxis is better than treatment It is easier to prevent obesity than to cure it The family physician should encourage patients to weigh themselves and keep their waist measure from increasing The treatment of any type of obesity lies in the correction of the disproportion between the intake and expenditure of energy To that end we may restrict food consumption and increase bodily activity The treatment is therefore essentially *dietetic* and *hygienic* Drugs are indicated for the complications only For success in treatment the patient s cooperation is essential No one can be satisfactorily reduced who does not wish to be It should be remembered that most fat persons though they may not admit it take delight in eating Food intake with them has fallen under the head of habit instead of instinct With the physician s help the habit can be gradually broken and the patient satisfied with an adequate instead of an excessive amount of food In women a desire to reduce often springs from vanity and in either sex this desire may be stimulated by a thorough explanation of the dangers of corpulence

The *indications* for a reduction cure depend on *several factors such as the patient s* age (reduction cures are less worth while in the elderly) the degree of obesity and the existence of complications In the slightly overweight otherwise healthy subject the indication may be for the regulation of diet and exercise only to the point of preventing further gain Sometimes the forbidding of candy alone or of excess butter cream sugar or bread will accomplish this In the somewhat more obese but still otherwise healthy patient the regulation must be more strict and a loss of weight sought The physician *must follow his patient until* the desired reduction has been achieved and thereafter guard against a recurrence He must decide upon the desirable amount and rate of loss in weight In the former he will be guided by standard figures for the weight of normal persons The rate of reduction will depend on the degree of obesity In marked grades it may be as rapid as three to four pounds a week In mild or moderate grades it need not be so rapid At the beginning of a reduction cure there is apt to be a rapid loss of weight chiefly due to water loss *Also as the reduction goes on there may be alternating periods of loss and absence of* loss due to fluctuation in water excretion and storage

A variety of reduction diets has been proposed None possesses any unique virtue The dietetic indication is simply to decrease total fuel intake without destroying the proper balance of the ration or depriving the body of vitamins The amount of protein allowed may be liberal and seldom should be reduced below 60 to 70 Gm A restriction below that might lead to the destruction of body protein thus weakening the patient The restriction should be chiefly in fats and the concentrated carbohydrate foods sugar and breadstuffs Fruits and the low carbohydrate vegetables are invaluable since through their bulk they not only reduce the pangs of hunger but also supply certain vitamins The physician with the use of food tables must plan the diet to meet the requirements of the individual patient In extreme grades of obesity Newburgh advocates diets as low as 300 calories per diem and commonly uses ones of 450 calories made up of 60 Gm of protein 10 Gm of fat and 30 Gm of carbohydrate It may be *desirable to increa e such diets to 600 or* 800 calories after a month or two in order to prevent ketosis which will occur in very obese young persons when they become really active These low diets should be reinforced with vitamins Less drastic reduction diets of 1200 or 1400 calories can be continued for long periods if accessory food substances are supplied in adequate amounts A program of gradually increased exercise should be combined with diet restriction Prolonged and gentle exercises are better than short violent ones

Thyroid will reduce weight by accelerating metabolism but there is the undesirable feature that symptoms of hyperthyroidism may also be produced Ordinarily, therefore thyroid should be used for reduction only when the basal metabolic rate is low Dinitrophenol has been widely heralded as the ideal reducing agent It raises metabolic rate and so causes reduction usually without un

pleasant symptoms It can, however, produce serious even fatal toxic injury, and consequently its use cannot be recommended

Amphetamine sulfate (Benzedrine sulfate) has recently become a popular drug for weight reduction Amphetamine appears to reduce weight by decreasing the patient's desire for food The dose is 5 to 10 mg twice a day Because of its stimulating effect and its tendency to produce insomnia the drug should not be taken late in the day

It has been found lately that rapid weight *losses sometimes produce or precipitate* thyrotoxicosis

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UNDERNUTRITION

(*Thinness Inanition*)

Definition —Undernutrition is the physical state resulting from the failure to ingest assimilate or utilize any or all of the substances essential for normal body metabolism Undernutrition may or may not be associated with thinness (subnormal body weight) and is therefore not to be considered simply the opposite of obesity When thinness alone is present the nutritional defect is due to inadequate caloric intake or to interference with the absorption and storage of energy supplying and fat forming foods Usually undernutrition is not confined to a single deficiency and lack of several or many food elements is detectable

Incidence —Recently numerous studies have led to the impression that a suboptimal nutritive state is much more common than previously recognized No general statistics are available since there have been no complete surveys of the population and the criteria for diagnosis have varied widely

Etiology —Nutritional deficiency may be due to inadequate intake defective absorption excessive destruction or elimination of one or more necessary food substances The materials required for optimal health and efficiency include carbohydrate fat protein the vitamins and certain minerals

Inadequate Intake —Many diets in America are deficient in thiamine (vitamin B_1) *nicotinic acid (niacin)*, ascorbic acid and calcium, resulting in recognizable clinical deficiency states, even in the presence of adequate caloric intake and normal body weight This is the result of economic factors in some instances but more often is caused by poor food selection due to habit or ignorance with consequent excessive intake of refined cereals white bread and sugar and neglect of whole wheat products fruits vegetables and milk Failure of intake of the necessary foods may result from organic disease causing inflammation or obstruction of the alimentary tract, vomiting nausea or anorexia Loss of appetite is a frequent symptom in many organic and functional disorders and is common in certain psychotic and psychoneurotic states Thus the clinical picture in a number of diseases may when food ingestion is insufficient be complicated by the development of a general or specific nutritional defect When intake is inadequate in only one of the essential constituents of food a characteristic disease picture may occur such as scurvy due to lack of ascorbic acid or hypochromic anemia due to lack of iron In instances of more or less general undernutrition the clinical syndromes characteristic of several vitamin mineral or other food deficiencies may appear together

Inadequate Absorption —Chronic diarrhea is the commonest factor interfering with absorption and assimilation of nutritive elements Other factors in this category are the absence of important enzymes (*e g* lack of pancreatic lipase resulting in steatorrhea) Other examples are the poor absorption of iron in the absence of adequate gastric hydrochloric acid and poor calcium absorption with deficient vitamin D

Increased Metabolism—When intake and absorption are enough for average normal requirements but cannot satisfy metabolic demands in special circumstances a relative deficiency exists which may often be corrected by increasing the amounts ingested To the basal caloric requirement for adults one must add not only calories in proportion to activity but an additional supply of vitamins and minerals Children require large amounts of energy foods plus liberal protein iron vitamin D and calcium if activity and growth are to be provided for and anemia and rickets prevented Pregnant and lactating women require more calcium and phosphorus than nonpregnant women because of the demands of the fetus or nursing Weight loss and vitamin deficiencies may occur in prolonged fever or thyrotoxicosis because of the accelerated metabolism Chronic inactive low grade infections such as tuberculosis chronic tonsillitis and chronic arthritis may keep a patient underweight even in cases where there is no fever In such instances undernutrition is presumably due to the effect of toxins on the metabolism Patients with diabetes become depleted of carbohydrate stores lack energy and become thin as the result of prolonged glycosuria Uncontrolled diabetics must utilize large amounts of body fat for energy and thus lose weight

Pathologic Physiology.—Since the possible types and causes of undernutrition are numerous and complex in nature there are no patterns of physiologic or chemical disturbance common to all cases Certain general considerations are nevertheless pertinent Foodstuffs may be classified according to their functions (1) as structural or supportive material (bone cartilage skin connective tissue stroma of individual organs and cells) (2) as fuel (for body heat for muscular activity and work as well as for the energy for numerous complex intermediate metabolic processes) and (3) as catalytic substances or chemical regulators

Most foods fall into more than one of these three categories By far the greatest proportion of carbohydrate is used for fuel but some is used in the production of special conjugated proteins in cartilage Some carbohydrate apparently is needed for certain enzymes Fats are primarily used for fuel but furnish some structural support Proteins are most important as structural material but are also important in the formation of enzymes and hormones and thus may also furnish catalytic substances and chemical regulators Protein can also be used as fuel when other fuel supplies are deficient or when protein is present in excess Calcium is used primarily to build bone It also acts as a catalyst in blood clotting and as a chemical regulator of neuromuscular activity Vitamins are essential food substances not utilized in structure or as fuel but as catalysts in certain important metabolic reactions Nicotinic acid for example becomes a component in two important coenzymes coenzyme I and coenzyme II both concerned in glycolysis and tissue respiration

With these functions of foods in mind it is evident that a deficiency in any single nutrient is apt to be reflected by more than one physiologic or chemical disturbance Nevertheless when the lack is chiefly of one food element certain typical changes may predominate These are presented in Table 1

Optimal nutrition includes not only provision of the materials essential for structure fuel and chemical regulation but for storage of certain reserves against unusual demands During an emergency such as fever vomiting or diarrhea fuel requirements will be met but if the fuel requirement exceeds the caloric intake for any prolonged period some of the energy must be supplied from body stores of glycogen and fat The patient may then become thin no matter what the cause of the negative energy balance When food intake is persistently insufficient to compensate for metabolic demands a chronic poorly nourished state is to be expected

In certain instances patients may remain thin when the caloric content of the diet seems more than enough to induce weight gain In the absence of an increased basal metabolism or of a digestive or absorptive disorder it must be concluded in such cases that the total metabolism exceeds the intake All careful metabolic studies support this conception which is only the application to human metabolism of the first law of thermodynamics Thin persons who are otherwise healthy often can be shown to expend more energy at work and in restless

movements and to relax less completely and sleep less soundly than normal persons having the same basal metabolism and body measurements When appetite and food intake remain excessive but weight loss progresses two possible explanations must always be considered hyperthyroidism or diabetes mellitus Failure to gain weight or steady weight loss may occur from any prolonged fever, for example in tuberculosis or brucellosis

ure Specific signs of lack of certain food elements may be present, e g osteoporosis with fractures of bone or collapse of vertebrae as the result of calcium lack soft bleeding gums and hemorrhages into the skin due to deficiency of ascorbic acid, dermatitis and glossitis of pellagra

In many instances the pathologic picture resembles closely that of pituitary cachexia (Simmonds disease) It seems likely that the pituitary failure may be primary in cer-

TABLE 1 —RESULTS OF INADEQUATE DIET

FACTOR LACKING	FOODS LACKING	RESULTS
Calories	Carbohydrates fats	Thinness lack of energy failure to grow
Protein	Eggs meat milk wheat corn rice peas beans	Muscle wasting hypoproteinemia edema
Calcium	Milk	Defective bones and teeth rickets osteomalacia and tetany in pregnancy
Vitamin A	Green vegetables carrots tomatoes milk eggs butter fish liver oils sweet potatoes	Xerosis of conjunctiva and cornea night blindness follicular hyperkeratosis
Vitamin B_1 (thiamine)	Whole cereals milk meat (especially liver and pork)	Beriberi polyneuritis
Vitamin B_2 (riboflavin)	Milk eggs liver green vegetables	Cheilosis glossitis ocular disorders
Nicotinic acid (niacin)	Milk lean meat liver	Pellagra stomatitis glossitis dermatitis
Vitamin C (ascorbic acid)	Oranges lemons grapefruit tomatoes	Scurvy capillary fragility hemorrhages, anemia
Vitamin D (calciferol)	Fish fish liver oils milk eggs liver (sunlight)	Rickets osteoporosis osteomalacia
Vitamin K	Green leaves spinach cabbage kale cauliflower egg yolk liver	Prothrombin deficiency hemorrhages resulting from prolonged bleeding and clotting time
Iodine	Fish iodized salt	Goiter
Iron	Meat liver eggs beans prunes peas wheat oatmeal spinach	Hypochromic anemia especially during growth menstruation pregnancy blood loss
Extrinsic factor	Muscle meats eggs wheat germ liver	Hyperchromic macrocytic anemia

Morbid Anatomy —Extreme undernutrition may result in death within a short time Less severe degrees of nutritional failure may result in emaciation and weakness which may persist for years with loss of practically all body fat muscle atrophy and evidence of premature aging The skin becomes dry, inelastic and wrinkled the hair becomes dry and gray and falls out teeth become carious and are lost and there may be evidence of pituitary, thyroid and gonadal failure tain cases leading to anorexia prolonged inadequate food intake and failure of the other glands of internal secretion When prolonged undernutrition results from anorexia nervosa or from any condition preventing adequate food intake for a long time pituitary failure may occur as one consequence of the severely disturbed body metabolism Atrophy of the other glands of internal secretion may follow with such changes as amenorrhea atrophy of sex or

gans and low basal metabolism Experimentally pituitary changes have been produced by chronic inanition and pituitary changes may be found following deaths attributed to anorexia nervosa

Persons who are undernourished have decreased resistance to infection and their tissues heal poorly after trauma Therefore infections of the skin bladder kidneys and lungs are common and ulcers of the mouth gastro intestinal tract or skin occur frequently

Moderate undernutrition may be manifested only by scanty body fat if the deficiency is primarily caloric or by one or more specific anatomic defects when there is a lack of certain particular foodstuffs such as vitamins or minerals (see Table 1)

Symptoms —Mild or early states of nutritive failure do not produce the striking signs or symptoms of emaciation or of beri beri pellagra or scurvy Vague ill health may be the first warning Lack of energy easy fatigue irritability mental depression headache and insomnia may appear and the patient may be said to be neurasthenic or to be constitutionally inferior There may or may not be weight loss Loss of appetite and gastro intestinal disturbances such as vomiting and diarrhea may further reduce the intake of essential food elements The body stores become depleted Disturbances in biochemical reactions necessary to normal body metabolism soon result Functional evidence of certain metabolic derangements may become more evident *e g* nightblindness paresthesias or pains in the extremities suggesting specific nutritive deficiencies Later may appear anatomic lesions identifying the condition as due to a single or more often to a multiple nutritive defect When the typical gum changes and hemorrhages of scurvy or the muscle wasting hypoproteinemia and edema of protein deficiency or the classic bony softening and deformity of osteomalacia occur it is not difficult to identify the disorder Before definite physical evidences such as changes in the mucous membranes skin eyes bones muscles or reflexes occur however diagnosis may be difficult This is necessarily so because of the numerous combinations of symptom complexes which occur with various multiple nutritional deficiencies Single deficiency states are rare so when there are symptoms of one the evidence of others should be sought

Diagnosis —The detection of undernutrition to be most effective should be early before florid signs of nutritional failure appear Four successive stages may be distinguished (1) tissue depletion (2) biochemical disturbances (3) functional changes and (4) anatomic lesions History of dietary inadequacy failure to absorb failure to utilize or hastened destruction or excretion of one or more dietary essentials is valuable Poverty bad food habits chronic alcoholism or a psychic disorder may be suggestive of poor intake Gastro intestinal symptoms may imply absorptive failure A febrile or metabolic disease may cause enough increased utilization destruction or elimination of nutritive elements to cause nutritional failure

Tissue depletion may be advanced before symptoms develop Weight loss when accompanied by fatigue irritability headache insomnia and depression is especially suggestive Our present technics are inadequate for detection of nutritional deficiencies in the stages before definite signs and symptoms develop but progress in this respect is rapid Only deficiency of protein (hypoproteinemia) vitamin K (lengthened prothrombin time) and vitamin C (low whole blood ascorbic acid) are now detectable by blood examination prior to the development of anatomic lesions High blood pyruvic acid when accompanied by suggestive symptoms implies thiamine deficiency Biomicroscopic eye examination may reveal capillary invasion of the cornea (riboflavin deficiency) or changes in the conjunctiva (vitamin A deficiency) Chemical determination of serum calcium phosphorus and phosphatase may suggest vitamin D lack or insufficient intake of these minerals Study of the number and morphology of the red blood cells and blood hemoglobin measurements may disclose anemia from iron deficiency or lack of ' extrinsic factor X ray examination of bones and joints will reveal lack of development in undernourished children or distorted development as in rickets Evidences of osteomalacia osteoporosis or scurvy may be thus detected in adults The chief clinical syndromes and anatomic lesions occurring in various deficiency states are given in Table 1

TABLE 2.—RECOMMENDED DAILY ALLOWANCES FOR SPECIFIC NUTRIENTS

Committee on Foods and Nutrition National Research Council

	CALORIES	PROTEIN GM	CALCIUM GM	IRON MG	VITAMIN A* INTERNATIONAL UNITS	THIAMINE (B_1) † MG	RIBOFLAVIN MG	NICOTINIC ACID MG	ASCORBIC ACID † MG	VITAMIN D INTERNATIONAL UNITS
Man (70 Kg)										
Moderately active	3 000	70	0 8	12	5 000	1 8	2 7	18	75	‡
Very active	4 500					2 3	3 3	23		
Sedentary	2 500					1 5	2 2	15		
Woman (56 Kg)										
Moderately active	2 500	60	0 8	12	5 000	1 5	2 2	15	70	‡
Very active	3 000					1 8	2 7	18		
Sedentary	2 100					1 2	1 8	12		
Pregnancy (latter half)	2 500	85	1 5	15	6 000	1 8	2 5	18	100	400–800
Lactation	3 000	100	2 0	15	8 000	2 3	3 0	23	150	400–800
Children up to 12 years										
Under 1 year§	100/Kg	3–4/Kg	1 0	6	1 500	0 4	0 6	4	30	400–800‡
1–3 years	1 200	40	1 0	7	2 000	0 6	0 9	6	35	
4–6 years¶	1 600	50	1 0	8	2 500	0 8	1 2	8	50	
7–9 years	2 000	60	1 0	10	3 500	1 0	1 5	10	60	
10–12 years	2 500	70	1 0	12	4 500	1 2	1 8	12	75	
Children over 12 years										
Girls 13–15 years	2 800	80	1 3	15	5 000	1 4	2 0	14	80	‡
16–20 years	2 400	75	1 0	15	5 000	1 2	1 8	12	80	
Boys 13–15 years	3 200	85	1 4	15	5 000	1 6	2 4	16	90	‡
16–20 years	3 800	100	1 4	15	6 000	2 0	3 0	20	100	

Tentative goal toward which to aim in planning practical dietaries can be met by a good diet of natural foods Such a diet will also provide other minerals and vitamins the requirements for which are less well known Reprinted from the J A M A June 7 1941 page 2601

* Requirements may be less if provided as vitamin A greater if provided chiefly as the provitamin carotene
† One mg of thiamine equals 333 international units 1 mg of ascorbic acid equals 20 international units
‡ Vitamin D is undoubtedly necessary for older children and adults When not available from sunshine it should be provided probably up to the minimum amounts recommended for infants
§ Need of infants increase from month to month The amounts given are for approximately 6 to 8 months The amount of protein and calcium needed are less if derived from breast milk
¶ Allowances are based on needs for the middle year in each group (as 2 5 8 and so on) and for moderate activity

Prevention and Treatment —Prevention is greatly preferable to treatment Discovery of the cause of a nutritive defect and its elimination before there is evidence of disturbed nutrition is the most effective treatment When intake is insufficient correction of faulty food preparation or poor eating habits may be necessary From four to six small attractive meals are better than two or three large ones Insulin (5 to 15 units one half hour before meals) stimulates appetite in some cases Carminatives are occasionally effective Psychotherapy is frequently indicated Moderate regular exercise with proper recreation and rest are important

Wholesome natural foods should be selected as the source of calories since thus the required vitamins and minerals are more apt to be obtained Nutritionists have discovered widespread waste in the usual methods of food preparation Large amounts of valuable minerals and vitamins are often discarded in the outer coverings of fruits and vegetables and in the cooking water Faulty preservation or the heat of cooking may destroy vitamins Treatment must supply sufficient amounts of all essential nutrients (calories proteins fats carbohydrates minerals vitamins and water) When a patient is quite ill or has a greatly increased requirement he may be unable to ingest or utilize adequate quantities of the usual foods In such instances concentrates or crystalline substances should be employed in proper amounts as supplements to the diet Tube feeding or parenteral administration of the most important nutrients may be imperative in severe illness

Prevention of nutritional disorders is facilitated by remembering that the commonest dietary factors lacking are calcium iron vitamins A and D vitamin B complex ascorbic acid and proteins of high biologic value (containing the essential amino acids) The use of enriched bread (with added thiamine nicotinic acid and iron) should be urged upon persons taking inadequate amounts of whole cereal foods In estimating optimal nutrient intake (see Table 2) account must be taken of age, sex size muscular activity pregnancy lactation and growth An average normal adult should eat each day at least the following protective foods (plus carbohydrate and fat sufficient to supply the necessary calories) 1 pint of milk 1 egg 1 serving (3 to 4 ounces) of meat 3 teaspoons (15 Gm) of butter, 4 servings of whole grain bread or cereal 2 vegetables other than potato (one green) 2 fruits one of which is raw

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ACIDOSIS

Definition — Acidosis is the term usually employed to designate a reduction of the bicarbonates (alkaline reserve) in the blood below the normal level

Blood is a complex buffer solution A buffer solution is one to which considerable amounts of acid or alkali may be added with a minimum change in reaction (hydrogen ion concentration) The chief constituents of the blood contributing to its buffer qualities are the proteins hemoglobin bicarbonates phosphates carbonic acid chlorides free oxygen and ammonium salts Of greatest importance are the bicarbonates because of their relatively great concentration and the easily available base for the neutralization of acid radicals

A less common use of the term acidosis and of less importance clinically is in connection with an *increase in the hydrogen ion concentration* of the blood above the normal range The reaction (hydrogen ion concentration) of the blood depends not so much on the concentration of the bicarbonates and

other buffer substances as on the relative amounts or ratio of weakly dissociated acids and their bases Blood reaction is customarily reported as the logarithm of the actual value of the hydrogen ion concentration using the notation *p*H The normal *p*H range is between 7 35 and 7 45 Since the acid base ratio is the important factor in maintaining a hydrogen ion concentration within very narrow limits in order that the life of the cells may not be endangered the expression acid base equilibrium is frequently used in connection with the reaction of the blood and body fluids

Under average normal conditions of activity and food intake the acid waste products of metabolism are in excess of the basic The mechanisms for coping with this contingency are (1) the buffer quality of the blood which maintains a constant reaction chiefly by combining the acid radicals with the base of the bicarbonate the liberated CO_2 passing off through the lungs (2) the excretion by the kidney of a urine much more acid than blood and the consequent return of base to the body to form bicarbonate ready for transporting more acid to the kidney and (3) the utilization of ammonia to combine with acid radicals to be eliminated as neutral salts

Occurrence —Whenever the removal of base occurs through the intake or production of acid which exceeds the capacity of the regulatory mechanism acidosis results In normal circumstances the regulatory mechanism encounters no difficulty from food intake and the products of metabolism The most common cause of acidosis is the excessive production of betahydroxybutyric and acetoacetic acids by faulty fat and protein metabolism Less frequently other organic acids may be produced in amounts sufficient to produce an acidosis

In the event of a derangement of the regulatory mechanism *conditions of acidosis may* arise as the result of the retention of acid radicals Disease of the kidneys may lead to a retention of phosphoric acid sulfuric acid and possibly other acids and a reduced capacity to utilize ammonia in the excretion of acid radicals A severe acidosis may be brought about through the removal of base by way of the bowel in the diarrheal diseases particularly in children

So far as is known at present acidosis is of clinical importance only if severe Varying grades of acidosis may appear in a variety of diseases *The more important conditions* in which acidosis may be present are

Diabetes Mellitus —Acidosis is one of the most serious features of *diabetes mellitus* in fact it is usually the cause of death Owing to the inability on the part of the diabetic to burn glucose there is a production of the ketone acids in excess of the ability of the organism to utilize them completely

Childhood —*Cyclic vomiting in children* is often associated with the production of large amounts of ketone bodies and a marked lowering of the alkaline reserve A disturbance in the metabolism of fat and proteins may occur suddenly in a perfectly healthy child The production of ketone bodies may be considerable and the acidosis extremely grave This condition is usually *accompanied by gastro intestinal symptoms* vomiting diarrhea and slight fever In the diarrheal diseases of children marked acidosis may be due to either the production of excessive amounts of an unidentified acid or the loss of base through the bowel

Renal Disease —In the terminal stages of chronic nephritis a very marked lowering of the bicarbonate of the blood is occasionally observed Less frequently acidosis is encountered in acute nephritis

Asiatic Cholera —A severe acidosis occurs in Asiatic cholera probably due to excessive loss of base through the bowel

Varying grades of acidosis *usually* mild may be observed in the infectious diseases during starvation in anesthesia pregnancy the chronic diseases with cachexia shock burns and poisoning with methyl alcohol salicylates and carbon monoxide *It* is seldom of any clinical significance

Diagnosis —Only marked acidosis can be recognized clinically The patients complain *of headache* weakness drowsiness and eventually become hyperpneic The characteristic fruity odor of the breath due to the excessive production of ketone acids may frequently be noted There are few conditions in which *laboratory tests are* of greater service than in the diagnosis of acidosis The information thus obtained is most useful when there is a distinct lowering of the alkaline reserve which is still insufficient to

produce clinical symptoms Early recognition of this frequently makes it possible to prevent serious acidosis

The most useful and reliable test is the *determination of the CO_2 combining power of the plasma* according to the method of van Slyke The normal range is 55 to 65 volumes per cent Values between 40 and 55 volumes per cent are indicative of mild acidosis The range between 30 and 40 volumes per cent is important While not in itself dangerous it represents the stage immediately before clinical symptoms appear and is the period when wise therapy may prevent a more serious condition Hyperpnea headache weakness and general malaise almost always are exhibited when the CO_2 combining power is in the neighborhood of 30 volumes per cent As the blood CO_2 diminishes the hyperpnea becomes greater and the drowsiness increases until deep coma supervenes at about 18 to 20 volumes per cent While patients may recover after the alkaline reserve has been reduced to 10 volumes per cent this level is extremely critical The author has seen recovery when the combining power had been reduced to 8 volumes per cent

So far as is known at present an increase in the hydrogen ion concentration of the blood without a lowering of the alkaline reserve is of secondary clinical importance

Prognosis—That acidosis is an abnormal physiologic state which may appear in a variety of pathologic conditions and *not a disease* should be clearly appreciated The prognosis then depends to a considerable degree on the underlying cause Prognosis should be guarded in any case with clinical manifestations for the more marked the clinical signs and the lower the blood CO_2 the greater the danger to the patient An important factor in prognosis is the response to treatment

Treatment—In nearly all conditions in which acidosis develops in severe form there is a depletion of water and base in the body The basis of rational treatment then is the restoration as rapidly as possible of the acid base equilibrium and water balance to within normal limits The diseased states in which the acidosis occurs have certain additional individual indications

Acidosis in diabetes mellitus is by far the most frequent and important form encountered in medical practice Treatment of diabetic acidosis consists in (1) amelioration of dehydration which may be associated with varying degrees of circulatory collapse and impairment of renal function (2) combating ketosis and (3) control of the diabetes

Relief from the physiologic effect of dehydration is *imperative* This is secured by the administration of adequate amounts of fluid and base Large amounts of fluid are often necessary and saline solution which supplies base as well as water is the solution of choice Not infrequently as much as 5 to 6 liters of saline solution in the first twenty four hours may be required In uncomplicated cases of diabetic acidosis in coma with a plasma CO_2 of 20 volumes per cent or lower the intravenous injection of 2500 cc of solution made up of 2000 cc of 1 per cent salt solution to which is added 25 Gm of sodium bicarbonate dissolved in 500 cc distilled water should be given without delay At least one hour should be allowed for the administration Thereafter 1000 cc of 5 per cent glucose in 1 per cent salt solution should be given intravenously every three hours until the patient s clinical condition is markedly improved *i e* until he is out of coma there has been a rise in plasma CO_2 and blood pressure and he is able to take fluids by mouth Where the acidosis is less severe and the patient is not in coma sodium bicarbonate may not be necessary and the amount of salt solution required to restore normal water and base balance may be less Most failures in the treatment of diabetic acidosis are due to the administration of insufficient amounts of fluid In the writer s clinic where the effect on the circulation has been followed by frequent venous pressure readings no harm has been observed in uncomplicated cases as the result of large infusions of saline glucose solutions

Fluids by mouth or rectum are ineffective When administered by hypodermoclysis they are much less effective than by vein Fluids by mouth for comfort when the clinical conditions warrant it are advisable Where the condition is complicated by hypertension, known cardiac damage pneumonia and in old individuals the administration of large amounts of fluids must be given with caution The best guide to the propriety of

continuing with intravenous saline solution in large amounts is the venous pressure When pneumonia is a complicating factor, venous pressure is an unreliable guide and large infusions should not be given An elevated venous pressure to start with is discouraging and one that increases as the result of infusion is a danger signal Should there be no diuresis within three hours following the first infusion and the blood pressure remains low, 90 mm or lower systolic, a transfusion of 500 to 700 cc of blood is indicated

Combating *ketosis* is essential This is best accomplished by giving immediately while preparing for the saline infusion 40 units of insulin subcutaneously if the blood sugar is 0 3 per cent or over and the urine sugar is 4 plus Ten units of insulin should be given every hour thereafter until the urine sugar becomes 2 plus

Such *general measures* as keeping the patient warm with hot blankets or hot water bottles, clearing out the lower bowel by enema and gastric lavage if the patient is vomiting should be instituted There is no medical emergency where hour to hour watching and meeting the indications as they arise is so essential to success as in severe diabetic acidosis Even after the patient comes out of deep coma and may appear to be improving rapidly sudden relapses occur and immediate treatment is necessary

The reader is referred to the article on diabetes for direction concerning dietary control Since the ketonic acids are largely derived from fats and to a certain extent from proteins both should be kept low The author prefers to restrict the fats to 20 Gm and proteins to 40 Gm with a fairly liberal allowance of 150 to 160 Gm of carbohydrate for the first two or three days following severe acidosis Insulin should be administered in amounts adequate to keep the urine sugar free

The acidosis which occurs in recurrent or cyclic vomiting of children if severe is best treated by intravenous administration of the appropriate amounts of saline solution and glucose If the plasma CO_2 is below 25 per cent and there is marked hyperpnea 5 to 10 Gm of sodium bicarbonate should be added to the first infusion The reader should consult textbooks of pediatrics for detailed discussion of this subject

In acidosis due to diarrhea saline infusions are usually adequate to control the situation If, however, the acidosis is severe sodium bicarbonate should be included in the first infusion and repeated if necessary

The acidosis associated with the terminal stages of chronic nephritis seldom requires treatment If hyperpnea develops to a point of making the patient uncomfortable sodium bicarbonate in small amounts either by mouth or intravenously may be employed Large amounts of sodium bicarbonate should be avoided owing to the danger of producing alkalosis to the point of causing tetany Several deaths are reported following the administration of large amounts of sodium bicarbonate to patients with chronic nephritis

Readers are referred to more comprehensive articles for a discussion of the theoretical consideration of the subjects where reference to the extensive literature may be found

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ALKALOSIS

Definition—Alkalosis is the term employed to designate an increase in the bicarbonates of the blood above the normal level or an abnormal increase in the pH of the blood due to the loss of carbonic acid Reference may be made to the general discussion of the buffer systems of the blood in the article on acidosis

Occurrence—When alkalis are ingested or administered in amounts which cannot be eliminated by the kidney or bowel at a rate to prevent accumulation in the blood alkal

osis results On the other hand if the acid radical chlorine is eliminated from the body in excessive amounts the sodium thus released combines with carbon dioxide thereby increasing the bicarbonate in the blood Carbon dioxide may be lost from the blood through hyperventilation and in this manner reduces the acid in proportion to bicarbonate which results in an increase in the *p*H or an uncompensated gaseous alkalosis

Alkalosis of clinical importance is observed in patients who have received large amounts of alkali for therapeutic purposes as in the treatment of peptic ulcer or in combating acidosis Several instances of death following the administration of large amounts of alkali to chronic nephritics have been reported Before the introduction of insulin the writer observed several patients with diabetic acidosis who had received sodium bicarbonate in amounts sufficient to produce a high grade alkalosis in the presence of a ketosis Severe alkalosis may be produced by prolonged vomiting either due to obstruction or of neurotic origin and occasionally the condition is seen due to frequent gastric lavage Hyperventilation as a cause of alkalosis may be voluntary due to hysteria or as the result of a lesion in the brain

Diagnosis —Mild grades of alkalosis seldom produce symptoms As the condition increases in severity the patient may become restless irritable and excitable until finally *tetany* supervenes with the exhibition of Chvostek s and Trousseau s signs and the characteristic response of the neuromuscular system to galvanic current The signs and

symptoms of alkalosis are the same irrespective of the underlying cause The plasma CO_2 is the most reliable guide to the degree of alkalosis present except in cases of over ventilation

Treatment —Rational therapy is directed toward the correction of the disturbed acid base balance and dehydration when present Therefore treatment will vary with the underlying condition which produces alkalosis If due to excessive alkali ingestion obviously the alkali should be discontinued If the condition has reached the stage of tetany an intravenous injection of 500 to 1000 cc of 1 per cent saline solution repeated within an hour if necessary, will control the situation Forcing fluids by mouth will facilitate the excretion of the excess alkali in the blood An alkalosis produced by vomiting in which there is loss of chlorides and marked dehydration should receive an intravenous injection of 1000 cc of 1 per cent sodium chloride solution repeated every three hours so long as necessary Alkalosis due to overventilation of neurotic or central origin is relieved by rebreathing a 5 per cent carbon dioxide oxygen mixture

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DISEASES OF THE DIGESTIVE SYSTEM

INTRODUCTION

THE great frequency of disorders of the digestive tract is due to the high incidence of primary *organic disease of these organs* and even more to numerous reflex or functional disturbances Gastro intestinal symptoms may be the initial or outstanding manifestations of such diverse diseases as scarlet fever intracranial tumor, pulmonary tuberculosis psychoneurosis or a senile depression It is thus impossible to separate gastro enterology from general medicine The newer developments in this special field however have been so important and have occurred so rapidly that a considerable degree of necessary and to a certain extent, desirable specialization has occurred Nevertheless the general practitioner is the first and only physician to meet and deal with the great bulk of the digestive disorders hence it is important for him to understand them well The *organic diseases* are of all types infections parasitisms intoxications deficiency states metabolic abnormalities benign and *malignant neoplasms, and others* The so called *functional disorders* are less tangible but no less real In general they may be 'reflex' toxic' emotional' or psychogenic" in origin It is very easy to quibble about names and definitions Perhaps a few simple examples will best serve to illustrate the meanings intended The nausea and vomiting of an intracranial tumor is obviously of central origin the nausea and vomiting of pregnancy is probably reflex although hormonal and emotional factors may be operative the emesis induced by ipecac and the diarrhea induced by castor oil are 'functional' although obviously attributable to a specific exogenous irritant the diarrhea of fear seems purely emotional in origin The gastro intestinal symptoms accompanying chronic states of fear anxiety tension and conflict are numerous bizarre and in one form or another ever present In practice the "functional' and the 'organic often co exist In the digestive tract it is particularly easy to argue if one wishes to do so for the interrelationship of the two, for the 'functional as a cause of the 'organic as for *instance in peptic ulcer* or ulcerative colitis In therapy, the functional may at times be entirely or almost entirely, disregarded usually it is of considerable importance and very frequently it is all important Not infrequently the organic may be disregarded The problem of the practitioner is to determine the cause of the patient s illness to cure the illness if possible and to prevent future illness

The *methods of examination* in digestive tract disease are the usual ones of medicine A good *history* is the first essential It should include an analysis of the distress peculiar to the acute attack or the chronic complaint with its relationship to the normal activities of life such as meal taking bowel habits menstrual periods exercise and so forth it should contain an inquiry into the function of other organs and systems the state of the appetite and the weight and it should include an evaluation of the individual in respect to his work his home his social relationships—in short a detailed appraisal not merely of the patient s symptoms but of the patient himself of the environment and of his emotional adjustment to the environment The *physical examination* is important but frequently not nearly as much so as the history

Laboratory procedures of all kinds may be important Those incident to any complete examination include complement fixation tests for syphilis erythrocyte and leukocyte counts hemoglobin determinations and urinalysis In addition the symptoms and findings may call for such investigations as a study of the spinal fluid careful appraisal of renal function chemical determinations of various constituents of the blood serum such as the carbon dioxide content the *p*H the chloride glucose urea nitrogen calcium cholesterol bilirubin or protein content and tests for the presence in the serum of specific

antibodies such as those for *S dysenteriae* or *B melitensis* The cost of these procedures is considerable it is neither necessary nor wise to order them routinely Judgment and knowledge are necessary in order to know when to obtain them and properly to understand and interpret them once they are made The same statement may be made with regard to the analyses more directly related to the digestive tract It is helpful to know whether the stomach secretes acid or not because of the extreme rarity of (a) pernicious anemia without achlorhydria and (b) benign ulcer with achlorhydria but emphasis on variations in gastric secretion as a cause of dyspeptic symptoms is erroneous The histamine test is simple to perform and may be a routine feature of the gastro intestinal examination in certain cases Similarly tests for the presence or absence of occult blood in the feces provide evidence for or against the diagnosis of gastro intestinal neoplasm The benzidine test employed on feces obtained after three days of a meat free diet is very simple and practical A careful microscopic examination of the feces especially those obtained after the administration of magnesium sulfate and *not* contaminated by barium bismuth or oil is important in instances of suspected parasitism A microscopic examination of the duodenal content obtained by so called duodenal drainage may disclose the presence of *Giardia lamblia* but these can usually be detected in the feces Other conclusions often reached from the results of duodenal drainage are of questionable value

Numerous tests of liver function have been described some are worthless some are helpful none is completely satisfactory The various dye methods usually give results roughly comparable to the retention of bilirubin present The tests dependent upon metabolic functions in the hepatic cells are of some value such as the hippuric acid test and the glucose and galactose tolerances Alterations in the constituents of the circulating plasma are often found and may denote impairment of hepatic function such as a low prothrombin content a low ester fraction of cholesterol or a low serum albumin not attributable to protein loss The colloidal gold and cephalin flocculation tests are dependent apparently upon qualitative alterations in the serum globulin resulting from disturbances in hepatic cellular metabolism

The *x-ray* is without question the most important method for the diagnosis of disease of the digestive tract The accuracy of skilled workers using the best equipment is phenomenal the reliability of untrained men using inadequate equipment is of course much less Errors consist of false positive diagnoses and of failures to find the lesion present Some of these errors are permissible for the method does have its limitations However there is a great need for more and better trained radiologists and for better machines Modern mucosal relief technic using so called spot films" with the fluoroscopically aimed exposure has greatly advanced the examination of the esophagus stomach duodenum and small intestine The air and barium double contrast films of the colon disclose in exquisite detail the finer alterations in the mucosa of that organ The methods perfected are splendid they must be used by trained workers they must be made more available The clinician however carries the final responsibility he must evaluate carefully all the evidence In the examination of patients with continued abdominal complaints whether mild or severe the roentgenologic examination particularly of the upper digestive tract should be omitted rarely if ever The cholecystogram and the barium enema while important are perhaps less essential as routine procedures

The *endoscopic methods* provide the only nonsurgical means for the direct inspection of the inner organs They rank in terms of the objective evidence provided second only to x rays Esophagoscopy is the most difficult of these procedures and the most hazardous it should be performed only by those properly trained and only when a definite indication exists Gastroscopy using the flexible instrument (Schindler) is a comparatively safe procedure but interpretation may be difficult Consequently it also should be carried out only by those well trained Proctoscopy is relatively safe requires the minimum of training and is of great value Benign and malignant neoplastic lesions of the rectum and rectosigmoid are very common are often beyond the tip of the examining finger and may be difficult to demon

strate roentgenologically The proctoscopic pictures of amebic dysentery nonspecific ulcerative colitis and lymphopathia venereum are usually quite typical The peritoneoscope is the newest of the endoscopic procedures and in trained hands seems to be of considerable value in selected cases

Two facts should ever be borne in mind by those dealing with chronic disorders of the gastro intestinal system first that more people die of neoplasm of the digestive tract than of any other system (in 1938 the deaths from cancer of the digestive tract and peritoneum comprised 47 per cent of the total cancer mortality) and second that many of these deaths could be prevented by earlier diagnosis and earlier operation

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DISEASES OF THE MOUTH

Infectious Diseases—The specific infectious diseases are accompanied by characteristic lesions in the mouth Tiny white spots surrounded by a red areola (*Koplik s spots*) are seen upon the inner surfaces of the cheeks and lips before the appearance of the rash of measles In scarlet fever enlarged fungiform papillae of the tongue protrude as scarlet points through the white coating causing the *strawberry tongue*

The *smallpox eruption* and *chickenpox* vesicles regularly appear upon the lips tongue palate and inner surfaces of the cheeks In about 7 per cent of cases of *typhoid fever* small ulcers appear upon the fauces

Mucous membranes are involved in all stages of *syphilis* Chancre of the lip or tongue appears as a sluggish painless ulcer with infiltrated base healing with slight deformity In the secondary stage the throat is injected and mucous patches appear on the tongue buccal surfaces and lips At the angles of the mouth condylomata occur Late in the disease gumma of the tongue begins deep beneath the middle of the dorsal surface and soon breaks down to form a sharply punched out ulcer The tongue is often shrunken smooth and harder than normal while the smooth atrophy of Virchow may be felt on the posterior surface Gumma of the lip is similar to that of the skin, gumma of the hard palate causes necrosis of bone and perforation Extending from the lips there may be rhagades or their scars

Tuberculosis is derived from milk, from tuberculous sputum or from extension of *lupus vulgaris* from the face The lesions are most frequent on the lips the edges of the tongue and soft palate Several small yellowish nodules appear at once ulcerate and gradually enlarge About the ulcer there are usually a few tiny nodules The discharge is thin and blood tinged and contains *tubercle bacilli* Healing is very slow

Yaws occasionally attacks the mucous membranes of the mouth late in the secondary stages and appears usually in the form of ulcers The characteristic frambesioid lesion has a tendency to profuse growth about the lips and nose *Gangosa* is a destructive ulcerative process which begins in the soft palate and slowly involves palate, nose lips and even the eyelids Recently it has been found that the causative organism is the same as that of yaws and responds to the same treatment

Rhinosporidiosis is due to infection by a phycomycete the *Rhinosporidium seeberi* which may be associated with cattle Lobulated masses of considerable size likened to a large cock s comb develop on the pharynx lips nose, eyelids and occasionally on the genitals and skin They must be cleanly excised preferably by electrocautery The native treatment—application of a mixture of lime and tobacco—*is said* to be effective

Espundia is the tertiary stage of American leishmaniasis Ulceration of the mucous membranes of the mouth proceeds to destruction of cartilage and bone and resulting deformity Hyperplasia may occur and then lobulated masses develop about the nose and lips *Verruca peruviana* of the cutaneous type occurs as profusely on the mucous membranes as upon the skin The red warty looking tumors usually ulcerate later *Foot and mouth disease* is transmitted from cattle Its rash occurs as freely on the mucous membranes as on the skin the vesicles in the mouth soon becoming superficial erosions which heal in a few days without scar *Leprosy* of the cutaneous type in nearly all cases develops in the mouth and on the lips

and pharynx The macule and the nodule are the usual clinical manifestations

Inorganic substances absorbed in small amounts for variable periods of time may cause lesions in the mouth

Mercury through occupational or therapeutic use causes the condition known as ptyalism Earliest symptoms are a metallic taste with soreness of the teeth upon chewing Later increased secretion of saliva swollen tender gums which *bleed easily swelling* of the salivary glands and a foul breath appear In extreme cases ulcers appear the teeth loosen and fall out and the jaw undergoes necrosis If mercury is discontinued when early symptoms are noted no trouble ensues With greater intoxication it is advisable to use an antidote Sodium thiosulfate is administered intravenously in doses of 0.3 to 1 gram at intervals of three days and careful attention is given to diet

Bismuth in the form of paste for the dressing of sinuses made surgeons familiar with its toxic effects With its current use in the treatment of syphilis the 'bismuth line is again commonly seen Located at the gum margin it is blue black but less sharply defined than the lead line *Less frequently* there may be blackish plaques of variable size on the gums or cheeks punctate or diffuse pigmentation of the soft palate blackening of the filiform papillae of the tongue and the veins beneath the tongue As a rule pigmentation disappears within three months after cessation of bismuth administration

Stomatitis develops in about one-tenth of the cases and its severity varies directly with the extent of pigmentation Gingivitis salivation and a foul breath are the mild manifestations With severe intoxication ulceration occurs about the third molars along the gum margin and in the floor of the mouth As infection develops anorexia and cachexia follow and fatalities have been reported

The use of a dentifrice and mouth wash of talc 85 per cent and sodium hexametaphosphate 15 per cent is reported to reduce the incidence of *stomatitis and even the pigmentation*

Iodine in any of its preparations may cause toxic symptoms Coryza is the most common but sometimes a coppery taste swollen mucous membranes soreness of the salivary glands and increased secretion of saliva follow its use Rarely with even minute doses sudden and alarming swelling of lips tongue and larynx may ensue Similar edema occurs with the *salicylates*

Radium—Intractable necrosis of the jaw is caused by ingestion of radioactive substances The radioactive material is deposited in the bones where it causes a condition *known as radiation osteitis Oral sepsis* is apparently responsible for the necrosis by adding infection to bone already the seat of disease Symptoms may not occur for several years after exposure The diagnosis is made during life by examination of the expired air for radium emanation using an electroscope or for the alpha particles by a scintillation screen No known treatment is curative possibly patients can be kept alive until the life period of mesothorium has expired

Dilantin (sodium phenylhydantoinate) used as an anticonvulsant in epilepsy causes hypertrophy of the gums particularly when there is poor oral hygiene Of slow onset and development the first symptoms are soreness *swelling and bleeding of the gums* but later these structures become firm and so much hypertrophied that the teeth are nearly covered and there is trouble in chewing Vigorous massage of the gums from the beginning of treatment and later gingivectomy in stages make possible the continued use of the drug

Gingivitis occurs in workers exposed to *chromium* it may follow the therapeutic use of *gold* salts of *ergoapiol* of *phenolphthalein* and it is one of the symptoms of poisoning by maize smut (ustilaginism)

Absorption of *lead* leads to gingivitis and the appearance of a blue black line at the margin of the gums *Silver* absorption results in bluish pigmentation of the mucous membranes while *arsenic* causes brownish stains of the mucosae of the cheeks or palate *Acetanilid* used habitually causes cyanosis of the lips

Diseases of the Skin—Many diseases of *the skin are accompanied by lesions of the* mucous membranes The more frequent are

Erythema multiforme in its recurrent attacks and various types of skin eruption may be accompanied by a bullous eruption in the

mouth The bullae soon become shallow ulcers which reveal no characteristic micro organism

Lichen planus often attacks the mucous membranes weeks before skin lesions occur In mouth and tongue the lesion is papular noninflammatory, feels somewhat rough and looks like mucosa to which silver nitrate has been applied The recurrent acute outbreaks the itching and the distribution and angularity of the skin lesions serve to make the diagnosis

Pemphigus in all forms is associated with bullous lesions of the mucous membranes which may appear in successive crops for weeks before there are any skin lesions Mouth bullae soon rupture to form shallow painful erosions which are covered with a diphtheroid membrane

Dermatitis herpetiformis (hydroa) is a chronic recurring inflammatory disease of the skin in which small vesicles occur in the mouth These rupture to form bright red ulcers which heal rapidly Intense itching is the outstanding complaint

The pinkish scaly eruption of *lupus erythematosus* is accompanied by shallow erosions of the lips buccal surfaces or tongue in about one fourth of all cases There are few subjective symptoms As healing occurs there is considerable atrophy with formation of a bluish scar The diagnosis is made from the characteristic skin lesion

Pseudocolloid (Fordyce s disease) of the inner surfaces of lips and cheeks occurs as numerous small yellow noninflammatory masses scarcely raised above the surface There are no symptoms and no treatment is required

Several clinical types of *lipoidosis* are accompanied by mouth lesions The simple *xanthoma* on tongue or cheek is common, less frequent are the lesions accompanying xanthoma tuberosum multiplex extracellular cholesterosis Gaucher s disease and the extensive infiltration of tongue and gums of lipoid proteinosis

Deficiency diseases are accompanied by characteristic lesions of the mouth Swelling soreness and bleeding of the gums occur early in *scurvy* In severe cases there is ulceration the teeth may fall out the salivary glands and tongue swell and hemorrhages occur beneath the mucous membrane of the palate In *pellagra* the mucous membranes are reddened denuded of epithelium and may be ulcerated The tongue and gums are swollen while the former is coated and bright red at the tip and edges *Pyridoxin* deficiency also causes a glossitis with a purplish red color Soreness of the tongue is one of the earliest symptoms of *sprue* The tongue is red the epithelium is lost the filiform papillae are swollen and there may be small vesicles or ulcers Anemia and the bulky fatty stool are characteristic *Riboflavin* deficiency causes redness and irritation of the lips fissures at the corners of the mouth much like perleche and a fine sandy desquamation of the nose

The *Plummer Vinson syndrome* is probably an iron deficiency There are chronic cheilitis glossitis and pharyngitis with resulting dysphagia and occasional choking spells There appears to be a special liability to mouth cancer Other features are the hypochromic anemia and koilonychia

Diseases of the blood and of the spleen cause mouth lesions

The red, engorged almost to bursting appearance of the mucous membrane of the mouth in *polycythemia* is very characteristic

Bleeding from the gums is seen in *jaundice* from any cause but is frequent in hypertrophic cirrhosis and hemolytic icterus It also occurs in *Banti s* and *Gaucher s diseases* In *idiopathic aplastic anemia* or in the secondary types from *benzol poisoning* or *chronic infection* petechial spots are seen and bleeding from the gums occurs while in *purpura hemorrhagica* bleeding from mucous membrane of the mouth may be serious

Pernicious anemia in its early stages is accompanied by soreness with patchy redness of the tongue and buccal mucosa In the late stages the tongue becomes pale and flabby with marked atrophy of the epithelium Areas of slaty pigmentation are seen in some cases on the cheeks lips and edges of the tongue Pigmentation of the mucous membrane of the mouth occurs in disturbances of the chromaffin system such as Addison s disease and retroperitoneal growths and is associated with small papillomatous growths in *acanthosis nigricans*

In leukemia of either type there may be bleeding from the gums or the first sign

of the disease may be an intractable hemorrhage from the socket of a recently extracted tooth Late in the chronic forms or at the onset of the acute forms acute stomatitis frequently develops and progresses to ulceration Gingivitis and ulceration occur in *agranulocytosis*

SAMUEL BRADBURY

DISEASES OF THE GUMS TONGUE, LIPS AND TEETH

Halitosis —In some instances halitosis is caused by evident local oral or nasal pathology In other cases however according to Crohn and Drosd malodorous breath is due to indigestion faulty metabolism of fats, and may be corrected by a low fat diet usually with the help of daily saline laxatives

Oral Sepsis —The common sources of oral sepsis are *alveolar abscess* and *pyorrhea* rarely there are infected *radicular* and *dentigerous cysts* An alveolar abscess results from caries of a tooth destruction of the pulp and ascending infection of the root canal The abscess at the root tip points through the gum (a gum boil) or it may be chronic and cause no local symptoms Abscess may result from a pyorrheal pocket the tooth remaining vital

Pyorrhea starts with inflammation of the periodontal membrane and progresses to rarefying osteitis of the alveolar process osteitis may occur without external sign of infection Sepsis results from absorption of toxins and bacteria Devitalizing influences such as malocclusion badly fitted appliances and dental calculus account for some cases but the majority appear to be caused by a chronic systemic disorder

Pyorrhea and alveolar abscess are frequent and are potential sources of trouble Often there are no symptoms there may be however a subnormal health level and rarely such serious consequences as chronic arthritis infection of the heart valves or kidneys or of the blood stream

Teeth —The Research Council of the American Dental Association in summarizing the opinions of observers from all parts of the world concludes that the causes of dental caries are not understood It is generally stated that caries is a bacterial disease with typical lesions coming in characteristic places and with the initiating factor acid destruction of enamel But why there is more caries in women than in men why primitive man has so little until he adopts civilized habits and why some persons may with impunity neglect oral hygiene is not explained It is acknowledged that a method of prevention is not yet achieved and it is held that such may be expected only through diet At present the sweets are generally held to be the most deleterious food factor

Mottled enamel is characterized by a chalky blotched appearance of the permanent teeth which may later become brown and is caused by fluorine in drinking water Such teeth are far less liable to caries and it has been shown that fluorine in amounts not sufficient to cause mottling will radically reduce the incidence of decay Mottled enamel occurs all over the world and in nearly 400 localities in the United States

Stomatitis —*Catarrhal Stomatitis* —The causes of catarrhal stomatitis are digestive disturbances traumatism by hot or highly seasoned food and the excessive use of tobacco There are swelling redness and tenderness in the gums cheeks and lips The tongue is coated there is salivation and a bad taste Infants refuse to eat and may have slight fever and diarrhea The disease lasts from three days to a week Mild mouth washes should be used frequently or in infants gently applied on pledgets of cotton

Aphthous stomatitis (*herpes simplex fever blister canker*) is an acute nonimmunizing infectious disease caused by a filtrable virus which is latent in many people It is activated by infections such as pneumonia epidemic meningitis and malaria by digestive disturbances and during the menses The disease occurs frequently in some families during puberty and in women Small vesicles singly or in groups appear upon the lips labionasal fold under the tongue or at the base of the alveolar process In the mouth the vesicle ruptures and forms an ulcer 1 to 3 mm in diameter covered with yellowish exudate and surrounded by a hyperemic zone There are pain salivation slight fetor and healing in five to ten days Local treatment consists in mild mouth

washes and the application of camphorated phenol Smallpox vaccine is said to prevent the recurrence of this troublesome disease Four vaccinations are made by the multiple pressure method at intervals of two weeks unless a take occurs then the take is allowed to subside and the series is resumed

Ulcerative stomatitis is uncommon and develops in children more than four years of age or in adult inmates of institutions or jails Local devitalizing factors such as carious teeth and accumulations of tartar play a role in its etiology and it may be that institutional epidemics are caused by deficient diets

The disease begins at the margin of the gum with swelling redness and oozing of blood upon slight manipulation usually in front of the lower incisors or on the outer side of the molars The inflamed area becomes necrotic ulceration spreads along the free border of the gums to the cheek and lower side of the tongue and is covered with a yellowish adherent slough The nearby lymphatic glands are enlarged and tender there is marked salivation coating of the tongue with slight swelling and a putrid odor to the breath In the worst cases ulceration may extend to the alveolar process and cause loss of teeth and necrosis of bone A few cases in children progress to noma An exanthem may occur and be mistaken for measles (Osler)

Sufficient food including vitamins must be given to children by gavage if necessary preferably in the form of cool liquids or soft solids Carious teeth and necrosed bone should be removed Mouth washes of potassium permanganate (1 8000) should be used frequently The ulcers may be touched with silver nitrate

Gangrenous Stomatitis (Noma Cancrum Oris) —This disease is essentially a rapidly spreading gangrene which occurs in debilitated children two to five years of age usually after one of the infectious diseases

The first manifestation is an extremely offensive breath Upon the buccal surface gum or inner side of the lip is found a small ulcer covered with gray or black slough which spreads both laterally and in depth In a remarkably short time the skin over the cheek becomes brawny then red and tense finally black and broken Gangrene rapidly destroys a large portion of one side of the face and attacks the tongue palate and gums Pain and fever are not marked the child is prostrated and death occurs in five to ten days The few children who recover are markedly deformed Bronchopneumonia abscess of the lung and severe diarrhea are complications

Treatment consists in early and thorough excision of the gangrenous area by the electrocautery If the child recovers plastic repair of the face may follow Diphtheria bacilli have been cultured from the gangrenous area and whenever present large doses of antitoxin should be administered

Ulceromembranous stomatitis is the name given to infection of the gums by the fusiform bacillus and spirochete described by Vincent It is the 'trench mouth of soldiers Epidemics of the disease occur and fatalities are reported

The accompanying symptoms and appearance of the lesion are similar to those of ulcerative stomatitis although isolated patches upon the buccal surfaces tongue and palate occur The infection is obstinate difficult to eradicate and recurs frequently Diagnosis is made by examination of smears from the infected gums

Treatment is difficult and requires pains taking attention to detail It is important in all cases that the food be nutritious and especially rich in vitamins In ordinary cases after the slough is removed a paste of sodium perborate powder is applied to the ulcers and held in place five to ten minutes After removal of the slough usually by means of half strength hydrogen peroxide solution the mouth is packed with cotton rolls the ulcers dried and chromic acid in 5 to 10 per cent aqueous solution is applied they are then allowed to dry and are covered with compound tincture of benzoin Or after similar packing and drying freshly activated zinc peroxide or an 8 per cent solution of zinc chloride or a paste of finely powdered copper sulfate may be used The latter particularly must be carefully rinsed off before removal of the packing Another local application is neoarsphenamine 10 per cent in glycerin Neoarsphenamine intravenously in doses of 0 3 Gm for adults is used but is not effective

Parasitic stomatitis (thrush) is due to a fungus of the class of Hyphomycetes known as *Oidium albicans* It infects the mouths of debilitated infants or those whose mucous membranes have been injured by violent cleansing or by stomatitis It is seen occasionally in adults after a severe infection or in the late stages of chronic illnesses

The infant refuses to nurse or has difficulty in swallowing There may be diarrhea with irritation of the buttocks The mouth appears dry and scattered over tongue gums cheeks and lips are small white patches which look somewhat like milk curds and can be removed only with difficulty leaving an hyperemic area which may bleed slightly The diagnosis is made by examination of a fresh specimen The usual attack lasts but two or three days Occasionally the infection may extend to the esophagus and pharynx and rarely to the trachea lungs and skin of the fingers and face Systemic infection has been reported

Infected areas should be painted twice daily with 1 per cent aqueous solution of gentian violet

Dermatostomatitis (Ectodermosis Pluriorificialis) is a rare disease of children and young people the worst result of which may be blindness It is characterized by chill fever and headache profuse salivation conjunctivitis development of vesicles on the lips tongue and cheeks and later erythematous or petechial lesions on the hands

Ludwig's angina is a streptococcal infection of the floor of the mouth Onset is acute with marked constitutional symptoms Swelling under the jaw extends into the neck pushing the tongue upward and the hyoid bone down The disease is frequently fatal *Treatment* consists of free incision and drainage Tracheotomy is often necessary The sulfonamides are effective *if there is time for sufficient dosage*

Bednar's aphthae are small ulcers upon the posterior part of the hard palate which are caused by unnecessary roughness in cleansing the infant s mouth or from pressure of too long a nipple

Riga s disease develops in infants after the eruption of the lower incisors It is especially common in Italy There is an indurated grayish area on the frenum of the tongue which may ulcerate later The affection may last for months but finally disappears Treatment is unsatisfactory The indurated area may be excised or tincture of iodine may be applied periodically

Periadenitis mucosae necrotica recurrens (aphthae resistentia) is possibly based upon endocrine disturbance At intervals pin head size painful nodules appear in the mouth and upon the genitalia enlarge ulcerate and resolve in about ten days Sutton advocates sulfathiazole in large doses

Other Types of Stomatitis —The frenum of the tongue may be ulcerated from pressure upon the lower incisors during attacks of whooping cough

Stomatitis due to infection by the *diphtheria bacillus* and the *gonococcus* is rare

Lips —*Harelip* is a congenital deformity caused by failure of the frontonasal plate to unite with the lateral process In the more severe grades the palate is commonly cleft. If the child nurses properly operation may be postponed to the third month but if there is difficulty it is advisable to operate while the infant is in relatively good condition

Macrocheilia is usually caused by *lymphangioma* There is gradual painless enlargement usually of the upper lip sometimes with attacks of acute inflammation Radiotherapy has been successfully used in treatment The less common cause is hypertrophy of the mucous glands known as *cheilitis glandularis apostematosa* The lower lip is more commonly involved there is excess secretion of mucus and the enlarged glands may suppurate Each gland must be removed separately

Cheilitis —*Acute cheilitis* (eczema of the lips) is caused by wind cold sunburn the lip stick and the drugs contained in some tooth pastes The vermilion border of the lips is inflamed crusts and often fissures occur It may be necessary to hold together the edges of fissures with narrow strips of adhesive plaster but usually removal of the cause and the application of zinc oxide ointment suffice

Chronic cheilitis (keratosis labialis) has much the same etiology and treatment as leukoplakia and is discussed under that heading

Perlèche (cheilitis migrans) is an infectious disease usually seen in children Small

white patches or vesicles form at the corners of the mouth, later, fissures form and are quite painful Tinnerud has isolated fungi in many cases either cryptococcus or monilia Nutrition must be improved, the mouth kept scrupulously clean, the lesions touched with 2 per cent aqueous gentian violet solution and the area covered with zinc oxide ointment

Carbuncle of the upper lip may cause septic phlebitis of the facial vein with progressive involvement of the ophthalmic vein and cavernous sinus A small pustule with a wide zone of infiltration rapidly enlarges and breaks down There is fever and prostration Incision or excision are contraindicated In the early stages wet applications of boric acid are indicated

Tongue—Anomalies are *scrotal tongue* which is commonly seen and *bifid tongue* which is rare Defective development of the anterior portion produces a condition known as *tongue tie*

Macroglossia results from congenital lymphangioma There is difficulty in speech and in swallowing and if the tongue be of such size that it protrude constantly the external part becomes dry and fissured Gradually increasing enlargement is caused by growth of the lymphangioma and by repeated attacks of inflammation Protruding portions of the tongue are excised and the remaining part subjected to radiotherapy Enlargement of lesser degree may be treated by radiation alone

Geographic tongue is seen in children and in adults One or more small white or yellowish elevations appear gradually enlarge and desquamate in the center leaving red patches with broad white circular outlines The disease is obstinate and treatment is unsatisfactory

Hairy tongue (*black tongue*) occurs in adults A brown or black patch on the posterior dorsal surface of the tongue appears to be composed of coarse hairs about 1 cm in length They are hypertrophied filiform papillae and may readily be broken off There is no discomfort There is no agreement as to the causative organism The patch may disappear spontaneously to reform later A simple mouth wash should be prescribed

Median rhomboidal glossitis is a diamond shaped red irregularly surfaced patch on the upper midsurface of the tongue anterior to the *circumvallate papillae* It should not be confused with cancer

Acute glossitis may follow burns bites or *other injuries* or may develop during an infectious disease such as smallpox or typhoid fever Usually there are high fever salivation pain which is referred to the ears and swelling of the tongue The neighboring lymph glands are enlarged The tongue should be incised and cold applied

Burning tongue (*glossodynia*) is encountered in women of middle age With two exceptions the causes are obscure First is the electrogalvanic discharge which is said to occur between dissimilar dental fillings It results in complaints of tingling and burning of the tongue or cheek a salty taste, occasional nerve shocks and an erosion which will be located near the positive end of the arc Second is the *temporomandibular joint syndrome* (Costen) in which occur headache in the occiput and postaural regions deafness and tinnitus and burning of the tongue Through loss of the molar teeth and atrophy of the alveoli undue strain is thrown on the articulation between mandible and temporal bone with resulting irritation of the auriculotemporal nerve The complaints are alleviated by a properly built up denture which will restore the original line of the bite'

Moeller's glossitis is a superficial inflammation in which irregularly shaped very red patches appear on the tip or sides of the tongue There is burning or pain and sensitiveness to hot or spicy foods The condition is obstinate Nonirritating food and mild mouth washes are advised

Leukoplakia buccalis (*smoker's patch*) and *keratosis labialis* are seen in adults of middle age more than 90 per cent of the cases in men There may be but one or two small patches or the disease may involve most of the mucosa of the mouth and tongue Recent lesions are thin often crinkled and pearly looking older *ones* are creamy white and thick and will desquamate from time to time leaving a beefy red base Advanced patches are *indurated* become fissured or papillomatous and are associated with dryness of the mouth The pathologic change is essentially keratiniza

tion of the mucosa and sclerosis of the derma it is a defense mechanism

The cause is chronic irritation, the producing factors in order of importance are tobacco used in chewing or in a pipe carious or infected teeth the electrogalvanic discharge between dissimilar dental fillings or appliances highly spiced food and betel nut chewing In leukoplakia of the tongue 30 per cent of the patients have had syphilis it is not a factor in keratosis labialis or in leukoplakia in other areas (Sturgis and Lund) In their cases cancer of the tongue, lip or cheek developed twelve times as frequently as among the average population

Early lesions usually disappear upon cessation of irritation The patient must stop using tobacco hot or highly spiced food concentrated alcoholic drinks caustic drugs and the tongue scraper The dental mechanism should be carefully supervised and a mild mouth wash prescribed The thick creamy white lesions and the papillomatous or fissured lesions are dangerous and are best treated radically Excision with the electro cautery gives better results than radiation but both may be used Patients with a positive Wasserrmann reaction should receive antisyphilitic treatment

Tumors and cysts about the mouth may be of any variety

Epulis is a fibrous tumor of the gum It is soft usually pedunculated and may be lobulated Frequently it grows opposite the roots of carious teeth The mucous covering is easily injured and ulceration results Treatment is excision

Ranula is an obstructive cyst of the mucous or salivary glands under the tongue A translucent fluctuating usually painless mass is seen on one side under the anterior part of the tongue It should be excised

Torus palatinus an elongated hard smooth or nodular mass in the roof of the mouth is an exostosis of the palatal processes of the maxillae There is a familial tendency the mass usually appears during adolescence and gradually enlarges It does not become malignant but may assume such proportions as to disturb speech or interfere with proper fitting of a denture The bony mass is removed with chisel or dental burr

Cancer about the mouth causes 3 to 6 per cent of all cancer deaths 85 per cent of cases are in males most are seen after sixty five years of age, the rise in incidence beginning at forty five but there are cases in patients less than 30 years of age The lip is most frequently diseased then tongue and cheek there may be multiple tumors Predisposing causes are leukoplakia oral sepsis rough teeth or dental appliances use of tobacco fissures and scars and overexposure to sunlight

An indolent ulcer a papillomatous or nodular tumor, or infiltration about a fissure must be viewed with suspicion Early diagnosis is important Biopsy with the electrocautery knife confirms the diagnosis denotes the degree of malignancy and determines the radiosensitivity of the tumor Tumors of embryonal type metastasize early and are more sensitive to radium

Cancer when it starts is a local disease and is curable Its care is a surgical problem but the mutilating operation has been largely superseded by radiotherapy Radium is preferred for the local lesion and is applied by means of heavily filtered containers attached to a molded plaque for surface application or by the implantation of radium needles or radon seeds

Recovery depends upon the type and location of the tumor and the presence or absence of metastasis The best recovery rates are with cancer of the lip the lowest with cancer of the cheek The experience of Massachusetts is illuminating In all cancer cases six months or more had elapsed from the first symptom to consultation with a physician then proper treatment was not instituted for at least another six months

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DISEASES OF THE SALIVARY GLANDS

The secretion of the salivary glands may be increased or diminished The normal twenty four hour amount in the adult is between 1 and 1.5 liters, the curve of output rising sharply during meals

Salivation (*Sialosis Sialorrhea*) —A true increase is known as salivation and may amount to a daily output of as much as 10 liters although the average amount is be tween 3 and 4 liters

The causes of salivation in the order of frequency are

1 Drugs or poisons, such as mercury, iodine tobacco, bromides arsenic, potas sium chlorate pilocarpine copper and bis muth

2 Local inflammation from any form of stomatitis except thrush, from pyorrhea and alveolar abscesses, and from such diseases as scurvy, sprue purpura and the anemias

3 Local irritation from jagged teeth badly fitting dental appliances teething ranula epulis and salivary calculus

4 Infectious diseases, especially smallpox and rabies

5 Reflex stimulation from the stomach pancreas liver and uterus Salivation is espe cially frequent in diseases of the stomach early in pregnancy and occasionally is an early symptom of ovarian cancer

6 Diseases of the nervous system such as seasickness and car sickness hysteria and migraine and the more serious organic dis eases such as irritation of the *chorda tym pani* usually with paralysis of the seventh cranial nerve degenerative lesions of the basal ganglia as in *paralysis agitans* and *en cephalitis lethargica* irritation of the vege tative system *tic douloureux* and *tabes* with salivary crises

7 Idiopathic cases in which no cause can be found Most cases develop after shock or severe emotion, there is an acute onset variable duration and sudden cessation

Symptoms vary, but when large amounts of saliva are swallowed indigestion and vom iting ensue In many cases the speech be comes thickened and the taste disordered

Treatment is that of the cause Atropine controls excessive salivation and bromides allay nervous symptoms Radiation of the salivary glands is effective in reducing secre tion but may cause dry mouth

Xerostomia (*Oligosialia*) is deficient se cretion of saliva The severity of the condi tion varies it may be apparent only when eating or there may be such deficiency that mouth and tongue are completely dry Some times there is also dryness of the conjunc tivae and the nasal cavities

The local infection thrush and the fevers are accompanied by dry mouth The drugs belladonna and opium cause deficiency of secretion Mild degrees of xerostomia accom pany the dehydrating diseases such as di abetes mellitus diabetes insipidus cholera and chronic nephritis X ray therapy of the facial regions may result in permanent de ficiency of secretion But the reasons for severe types of xerostomia are obscure, the unusual cases occur in women of nervous temperament without other signs of ill health It is suggested recently that some cases of xerostomia are instances of avita minosis

The salivary glands may appear to be normal or they may be swollen and the ducts full of thick mucopus In severe cases the tongue lips and buccal surfaces become dry shiny red and fissured and the conjunc tival sacs contain thick ropy secretion

Treatment is unsatisfactory A glycerin mouth wash is useful Pilocarpine may stim ulate the salivary glands A prolonged course of vitamin B complex or nicotinic acid is worth a trial The teeth require careful su pervision

Inflammation of the salivary glands may be acute or chronic In any type except that following calculus the parotid gland is most often involved

Acute Inflammation —Aside from mumps acute inflammation (parotid bubo) occurs as a complication in several diseases These

are of three distinctive groups acute general infections such as typhoid and typhus fever and pneumonia, injury or disease of the abdominal or genito urinary organs, or after operation upon these structures diseases which interfere with the secretion of the salivary glands such as obstruction of the ducts facial paralysis or conditions which cause dry mouth

As a rule a single parotid is inflamed The onset is sudden with increase of the fever and toxic symptoms already present The gland swells becomes tense and tender, there is pain which is referred to the ear and interference with swallowing The swelling rapidly increases the overlying skin soon becomes red and shiny and in a few days fluctuation is present The infectious agent is usually Staphylococcus aureus The disease is serious and carries a high mortality

TREATMENT —The prevention of acute parotitis consists in scrupulous cleanliness of the mouth and the prevention of dehydration in postoperative and febrile conditions by the maintenance of a high fluid intake either oral or parenteral If inflammation develops an ice bag or a poultice should be applied Early x ray therapy reduces toxemia lessens suppuration and lowers mortality Should pus develop the gland should be incised with care to avoid the facial nerve and the large vessels

SYPHILIS may cause acute or gummatous inflammation Sixty five cases have been reported 22 occurring in the early stages 37 in the late stages and 6 in congenital syphilis The parotid was involved alone in 53 cases and 5 cases with other salivary glands There is gradually increased swelling and salivation but not much pain or tendency to suppuration Both the early and late forms respond to the usual antiluetic medication

Chronic inflammation is more frequently multiple than acute and may affect all the salivary glands The usual causes are mumps syphilis inflammation of the throat prolonged exposure to mercury iodine or lead and chronic nephritis Salivary calculi especially those lodged in the ducts may cause chronic infection As a rule the parotid glands are infected in glass blowers who have gaseous tumors There is impaired secretion and usually slight swelling which varies in degree from time to time

The possibility of calculi should be ruled out by examination and by x ray Otherwise the treatment is that of the assigned cause

Salivary calculi (*sialolithiasis*) develop in men about twice as frequently as in women Bacterial infection stricture from wound or inflammation and possibly foreign bodies are the usual preceding conditions In two thirds of the cases the calculus forms in the submaxillary gland or its duct The stones are composed mainly of calcium oxalate with smaller amounts of organic matter carbonates phosphates and magnesia They vary in size from a diameter of 3 to 30 mm The largest are found in the glands and are usually round or irregularly lobulated duct stones are of small diameter and oval

A calculus in the gland causes no *symptoms* unless it sets up inflammation but the patient may notice unusual swelling before this occurs Duct calculi produce symptoms when they cause obstruction There is sudden pain often of colicky nature usually felt in the floor of the mouth and relieved by a gush of saliva The swollen gland is readily felt and quite tender The stone may be found in the duct by palpation An x ray picture taken to avoid the mandible demonstrates the calculus

The *treatment* is excision

Uveoparotid fever is characterized by firm painless enlargement of the parotids with inflammation of both uveal tracts and low grade fever of several months duration Often there are bilateral facial paralysis deafness and tinnitus and in some cases polydipsia polyuria polyneuritis xerostomia glossodynia enlargement of other salivary glands and of the lacrimals and general lymphadenopathy with splenomegaly As this clinical syndrome is more carefully observed it is clear that it has many of the clinical features of and should be classified with Sarcoidosis

The etiological agent is unknown with negative tuberculin tests absence of acid fast organisms and general tendency to recovery it is probably not the tubercle bacillus Most patients with uveoparotid fever return to health but the uveitis leaves permanent visual defects

Mikulicz's syndrome, first described in 1888 is a symmetrical enlargement of first, the lacrimal then the salivary glands Cases

have been seen in which there is splenomegaly and local or general lymphadenosis some with normal blood, others with changes in the blood which are typical of chronic lymphatic leukemia A very few cases have been seen to change gradually from simple to more severe types, in others, there has been subsidence of the swelling after an acute infection The usual histology of excised tissue *is that of lymphoma After complete* extirpation of the glandular masses there is no tendency to recurrence nor to involvement of the lymphatic structures

The swelling progresses very gradually involving first the lacrimal glands then the parotids, submaxillaries, and the sublinguals In some cases accessory glands on the hard palate and the tongue share in the enlargement The picture is not always complete, the lacrimal glands may be involved alone or they or any one or more of the salivary glands may escape The glandular masses are firm smooth painless, not tender and not adherent to the surrounding structures

The patients complain of their appearance and of difficulty in vision caused by ptosis of the eyelids and interference with the movement of the eyeballs Excretion of saliva is *usually so* deficient as to cause difficulty in mastication and deglutition and diminution of excretion of the lacrimal glands causes irritation of the conjunctiva As a rule the *patient remains in good general* health

Of two male patients with typical Mikulicz's *syndrome* one had *general lymphadenosis* with biopsy showing lymphosarcoma the other recovered upon antiluetic medication A young woman with marked bilateral swelling of the parotid and submaxillary glands had also symptoms of hypothyroidism, the swelling disappeared upon thyroid medication A few cases are due to syphilis or tuberculosis but most can be ascribed to no definite cause Men are more frequently affected than women and while the disease occurs in children the usual age of onset is between twenty and forty years

Treatment —The internal administration of arsenic and potassium iodide has proved a satisfactory form of treatment in most cases Exposure to the roentgen ray has been successful Surgical removal of affected glands is advisable in selected cases

Tumors —Almost any type of tumor either benign or malignant, may develop in the salivary glands, and in 75 per cent of the cases the parotid is involved Forty two of fifty proved malignant tumors were found to be in *nearly equal proportions mixed* tumors or carcinoma or sarcoma, of twenty histologically benign tumors fifteen were of the mixed type

The tumor is first noticed as a small nodule in the gland tissue which may remain quiescent for years, then enlargement begins either slowly or rapidly The tumor may feel very dense or quite soft according to the type of the predominant tissue, it is rarely tender usually smooth but sometimes lobulated

The best *treatment* is early and complete excision followed by exposure of the area to the roentgen ray Local recurrence is frequent The recurrent growths are usually more malignant Metastasis is unusual

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DISEASES OF THE PHARYNX

Acute Pharyngitis (*Sore Throat Angina Simplex*) —INCIDENCE —Acute inflammation of the mucous membrane of the pharynx occurs in individuals whose *general* condition is poor or whose habits of life are faulty The incidence is higher in spring fall and winter than in summer

This disorder is *frequently the* initial or early symptom of some acute infectious disease such as acute coryza scarlet fever measles or influenza Early secondary syphilis of the pharynx *often resembles* acute pharyngitis

Etiology —Exposure to drafts and chilling of the body after violent exercise are frequent causes *Local allergic reactions* to certain fruits such as grapes strawberries or

grapefruit sometimes cause a condition resembling acute pharyngitis

Symptoms.—The disease may start with a slight cold or more frequently with a sensation of chilliness This is followed by dryness in the throat and irritation in the nasopharynx Soon the throat becomes painful and swallowing is difficult Examination of the throat at this time reveals a mucous membrane which is red swollen and covered with whitish mucus The general constitutional symptoms of a mild febrile condition are present In very mild cases the temperature may not rise at all Acute pharyngitis lasts from one day to two weeks and is usually self limited Not infrequently however the infection extends upward into the nasal cavities or downward into the larynx and trachea

Diagnosis—The fact that for some time (twenty four to seventy two hours) it may be the only local symptom of an acute infectious disease must be especially borne in mind when marked congestion of the throat is associated with severe general symptoms The condition in itself is not difficult to recognize

Treatment—Therapeutic measures should be of such a character as not only to hasten recovery but also to prevent recurrence of the disease The general physical condition of the patient must be determined the habits regulated suitably and any predisposing factors such as deviation of the septum infection of the sinuses or tonsils and dental pathology eliminated At the onset of an attack a laxative (preferably castor oil) should be administered and the patient put to bed Patients with fever ought to remain in bed until the temperature falls to normal those in whom the disease is afebrile may get up after the first twenty four hours

For local treatment there is nothing more satisfactory than irrigation of the throat with a solution of sodium bicarbonate (1 teaspoonful of soda in 1 quart of water) either hot or cold This may be supplemented by the application of an ice collar or cold compresses to the throat Local antiseptics are not beneficial in the acute stage and should be avoided A soft simple diet is desirable

If a hemolytic streptococcus be suspected or proved to be an etiologic factor in this condition the administration of sulfadiazine may cut short the disease If drugs of this type are used throat irrigations must be limited to normal saline solution Daily blood counts and urinalyses should be made It is usually advisable to hospitalize the patient

Chronic Pharyngitis (*Chronic Sore Throat*) —This is usually a disease of adults It frequently develops in individuals compelled to work in dusty unhygienic surroundings and in those who use the voice improperly and to excess Habitual alcoholics and smokers are also disposed to the disease The condition is often associated with general systemic abnormalities such as gout rheumatism and certain chronic diseases of the circulatory and respiratory systems

Types of the Disease—Chronic pharyngitis is of three types—the hypertrophic the atrophic and the chronic granular type The *hypertrophic type* is characterized by general thickening and congestion of the mucous membrane of the pharynx which is thereby rendered velvety in appearance The *atrophic type* is probably a late stage of the hypertrophic and is evidenced by abnormal thinness of the mucous membrane which is whitish glistening and at times wrinkled In the *chronic granular form* (clergyman s sore throat) the hypertrophic changes are particularly marked in the lymph follicles of the posterior pharyngeal wall and on the lateral wall behind the posterior pillars of the palate

Symptoms—The symptoms are a constant sense of irritation or fulness in the throat the dropping of mucus from the nasopharynx or its collection in the throat and at times difficulty in swallowing Some patients cough and develop the habit of clearing the throat

Complications—The chronic inflammation not infrequently invades the eustachian tube and middle ear so that deafness ensues Subjects of the disease are susceptible to laryngitis and inflammation of the trachea and bronchi

Diagnosis—Examination of the throat and nasopharynx with either direct or reflected light permits easy diagnosis of chronic pharyngitis In the granular type the rounded masses of lymphatic tissue are visible in the postpharyngeal wall and be

hind the posterior fauces of the palate In the atrophic form the mucous membrane is seen to be pale and glistening and at times covered with brownish crusts Coakley says that the cicatricial tissue left by an old syphilitic, tuberculous, or lupoid ulcer may at times be mistaken for atrophic pharyngitis but that this tissue has a white puckered appearance different from that of the mucous membrane of atrophic pharyngitis

Prognosis—The symptoms of chronic pharyngitis, while annoying are not incompatible with fair general health

Treatment—The treatment of this condition is both local and general The *general measures* consist in making the general health as good as possible Alcohol and tobacco should be forbidden and the patient taught to use the voice properly and not to excess Infected tonsils should be removed and any abnormal condition in the nose corrected, surgically if necessary All dental pathology should be eliminated Aside from irrigation of the nose and throat with alkaline solutions to remove tenacious crusts and mucus *local treatment* is best performed by the specialist The results are apt to be discouraging The success of treatment depends on the duration of the disease and on the possibility of relieving the underlying predisposing cause

Retropharyngeal Abscess—A retropharyngeal abscess is an accumulation of pus in the submucous connective tissue of the pharynx

Etiology—This occurs most frequently in infants and children between six months and four years of age, but, occasionally has been seen in adults The incidence is high in the apparently healthy infants of the poor Coakley states that tuberculosis rickets and inherited syphilis are predisposing factors Occasionally the disease is secondary to tuberculosis of the cervical vertebrae

Morbid Anatomy—The abscess is usually due to a streptococcus infection of the retropharyngeal lymph nodes in the submucous connective tissue of the pharynx These glands enlarge and later break down and form an abscess The pus may burrow beneath the mucous membrane so that at times a large abscess develops which seriously interferes with laryngeal function

Symptoms—The onset of a retropharyngeal abscess is manifested by fever irritability, and crying These symptoms are soon followed by difficulty in swallowing and refusal of the infant to nurse or take the bottle The cry at times is of a peculiar quacking character, described by Regnier as "le cri de canard" Dyspnea may occur and with the cough produce a syndrome resembling that of croup The temperature may be high, and, on account of the inability to swallow, emaciation is at times rapid and extreme If untreated the abscess may rupture spontaneously during sleep and cause death by suffocation or produce suffocation and fatal inanition without rupture When the lesion is not severe there may be no apparent symptoms except those of nasal obstruction and it is discovered only during the routine digital examination for adenoids

Diagnosis—The diagnosis of retropharyngeal abscess is usually easily made by inspection or palpation If the mouth is opened with a tongue depressor a smooth oval swelling is visible on the posterior wall which pushes forward the palate and uvula By digital examination this is found to be smooth and elastic and fluctuation is often easily obtained Symptoms of croup must be carefully distinguished from those of a retropharyngeal abscess

Prognosis—If the abscess is evacuated early recovery is usually good but if the patient is first seen in the later stages of the disease when dyspnea and prostration are marked death may ensue even after prompt draining of the lesion Tuberculous abscesses and those which follow vertebral caries are apt to end less favorably

Treatment—The only treatment is early incision to permit free drainage Most abscesses can be opened suitably through the mouth when the child is held by the nurse with the head lower than the body and the mouth wide open The incision should be made through the mucous membrane in the median line beginning opposite the larynx and passing upward toward the palate It is necessary to guard the blade of the scalpel with the finger or a piece of adhesive tape about ¼ inch from the point Care should be taken to avoid injury to the soft palate When the pus ceases to flow from the mouth

and nose the abscess should be gently pressed with the finger to remove any purulent material which may remain Since the cavity sometimes refills and must be redrained it is desirable to watch the child closely for a few days after this operation If dyspnea and weakness place the patient in danger speed is necessary, but under ordinary conditions there is no need of performing the operation very rapidly If a retropharyngeal abscess is suspected to be tuberculous in origin secondary infection is best avoided by external incision along the anterior border of the sternomastoid This procedure should not be performed by the general practitioner After evacuation of the abscess measures should be employed to restore the child to its normal condition Life in the open air and the administration of tonics such as cod liver oil iron and vitamins are desirable Usually the relief after evacuation is immediate

Angina Ludovici (*Ludwig s Angina Cellulitis of the Neck*) —Johnson has described angina ludovici as a more or less violent purulent and sometimes gangrenous inflammation of the tissues occupying the submaxillary region of the neck The characteristic symptoms are those of severe sepsis the formation of a hard tense brawny swelling in the submaxillary region great pain difficulty in speaking and swallowing and sometimes cyanosis and dyspnea caused by pressure on the larynx or by swelling and edema of the throat If unrelieved by early incision *the whole side of the neck becomes* red and hard the constitutional symptoms threatening and the local symptoms of interference with respiration alarming This condition is usually secondary to violent infection of the throat or tonsils or teeth usually by a streptococcus occasionally by a staphylococcus The prognosis is grave and the practitioner should seek early the advice of a competent surgeon

In addition to the treatment outlined above the administration of sulfadiazine is probably indicated

Neuroses of the Pharynx —Neuroses of the pharynx are motor and sensory The most common *motor neurosis* that known as *globus hystericus* is a spasmodic action of the motor nerves which causes the sensation of a lump in the throat and is usually associated with enlargement of the lingual tonsil or a lingual varicosity *Spasmodic contraction of the pharynx and esophagus* which causes swallowing of air with subsequent eructation, is occasionally seen in chorea The *treatment* of these conditions is mental with correction of the causative factor

Sensory Neurosis.—Anesthesia of the pharyngeal mucosa occasionally complicates general nervous disorders It is most common in hysteric patients

Hyperesthesia frequently accompanies chronic inflammation of the pharynx

Paresthesia (sensations of suffocation tickling itching or of the presence of foreign bodies) is not uncommon in the neurotic or insane

T Laurance Saunders

DISEASES OF THE ESOPHAGUS

Life without use of the esophagus for introducing food into the stomach is difficult and the value of it questionable Many of the diseases which affect this long and relatively narrow tube interfere with the passage of food into the stomach with resulting malnutrition or even starvation Therefore although relatively infrequent these diseases are of importance The earlier the diagnosis is made the more satisfactory are the results of treatment hence careful consideration *should be given to the two cardinal symptoms*—pain or difficulty in swallowing

Diagnostic Procedure —The symptoms presented by the patient are of considerable aid in diagnosing diseases of the esophagus The description of the onset progress or persistence of the pain or difficulty in swallowing is helpful A complaint of gurgling noises on swallowing the regurgitation of food on change of position or during sleep accompanied sometimes with a strangling sensation or even strangling on swallowing is of significance Hoarseness may be present if the recurrent laryngeal nerve is involved With surprising accuracy a patient may identify the level of the lesion in the esophagus

So little of the esophagus is available for inspection and palpation that physical ex

amination reveals little except anemia, loss of weight, the presence of a tumor mass in the neck, and enlargement of the spleen which occurs in certain instances

X-ray examination in many instances will establish the diagnosis, but direct inspection through the esophagoscope should be carried out in all doubtful cases Material for a biopsy may be secured through the esophagoscope

Congenital Abnormalities—The esophagus may end in a *blind pouch* within the thorax The lower end of the esophagus in such instances may be connected to the upper by a fibrous cord or be entirely disconnected Either of these pouches may connect by fistula with the trachea or bronchus These infants usually succumb in a few days from starvation although surgeons are continually struggling with the problem If a fistula exists pneumonia usually develops if the infant is kept alive by some artificial method of feeding A fistula may exist between the trachea and a patent esophagus

Congenital cysts occur in the wall of the esophagus which may or may not cause symptoms of obstruction

Congenital dilatations or *narrowing* or even pouches of the esophagus occur which may or may not give symptoms The narrowing of the esophagus may need dilatation at once or may not produce symptoms until after some years

The *esophagus may be congenitally* so short that the stomach protrudes through the diaphragm to meet it This type of *diaphragmatic hernia of the stomach* may or may not produce symptoms

Diverticulum—Diverticula are of two types One the so called *pulsion* or *pressure diverticulum* is usually a real hernia of the mucous membrane through the muscular coats but in a few instances some muscle fibers are included in the sac These herniations occur where there is some defect in the muscle coats or where these have been weakened by disease or trauma and are the more frequent The other type is a so called *traction diverticulum* which is a distortion of the esophageal wall due to contraction of scar tissue in surrounding structures which have become adherent to the wall of the esophagus

Pulsion Diverticulum—SITE—The commonest site is at the junction of the pharynx and esophagus (sometimes called pharyngo esophageal diverticulum) at which point the muscle coats often fail to surround the tube completely Another site is at the natural narrowing of the esophagus caused by the left bronchus as it crosses in front Still another site is at the lower end of the esophagus just above the diaphragm Such diverticula are called supradiaphragmatic or epiphrenic The diverticulum at the upper end of the esophagus starts as a slight bulge which gradually increases in size until a sac has been formed large enough when filled to be seen and palpated As the sac increases in size it distorts the lumen of the esophagus so that obstruction to the passage of food into the stomach occurs These diverticula usually occur in people more than forty years of age

SYMPTOMS—The symptoms vary from the sensation of a particle of food stuck in the throat to difficulty or inability to swallow When the sac is large enough for food to collect in it and decompose, foulness of breath accompanied by dryness and irritation of the mucous membrane and excessive secretion of mucus result *Regurgitation* from the sac with leakage into the larynx especially at night produces strangling *Gurgling noises on swallowing due to* a mixture of fluid and air in the pouch may occur

DIAGNOSIS—*On physical* examination a tumor mass may be felt on one side of the esophagus and the size of the tumor will *diminish after regurgitation* The diagnosis is usually made by x ray examination Should esophagoscopic examination be indicated care must be taken not to rupture the sac due to the esophagoscope entering the sac rather than passing down the esophagus In the early stages while the sac is small dilatation of the esophagus *below the* diverticulum may retard appreciably its enlargement When the diverticulum produces enough symptoms it should be *removed by* surgical procedure Diverticula of this type in the midthoracic region and at the lower end of the esophagus *usually do* not interfere with swallowing but other symptoms are essentially the same For the midthoracic *diverticula dilatation* of the esophagus below the lesion is about the only procedure

available For the diverticulum at the lower end of the esophagus the surgeons suggest hitching the bottom of the sac upright in the mediastinum so that such food as passes into it will drain out

Traction diverticula rarely cause symptoms of importance but should food accumulate in the bulge, dilatation of the esophagus below with a dilator passed along a previously swallowed thread seems the most satisfactory procedure

Inflammation —Lesions may occur in the esophagus during the course of many infections such as the primary lesion of syphilis the eruption of smallpox the ulcers of typhoid fever or tuberculosis and the reactions associated with various acute infections including glanders actinomycosis and diphtheria Usually these lesions masked by the other symptoms of the disease are of little practical importance Acute inflammation of the esophagus may be produced by chemical irritants or pus forming organisms Thrush is an important cause in children These inflammatory agents may reach the esophagus from the mouth or by extension from adjoining structures A catarrhal condition of the esophagus may develop from less severely irritating substances acting over a long period

Symptoms —Acute inflammation causes pain along the course of the esophagus burning beneath the sternum often difficulty or pain in swallowing and a marked increase in the secretion of mucus in the pharynx and mouth Vomiting may occur usually with mucus and blood mixed with the vomitus Extreme thirst is a common symptom Should the inflammation become so severe that rupture of the esophagus occurs the patient will show marked prostration and localized symptoms dependent upon the structure into which the rupture has occurred The general constitutional symptoms and febrile reaction will depend on the severity of the process

Diagnosis —A history of swallowing some irritating substance is an important aid in diagnosis It is undesirable to use instruments blindly in an esophagus which is acutely inflamed for fear of rupture X ray studies are usually not indicated If the diagnosis is not satisfactory careful inspection with the esophagoscope may be tried

Treatment —The treatment of acute inflammation of the esophagus consists in removing the irritating causes if persistent and in giving the esophagus as complete a rest as possible Oil or cool drinks may be administered by mouth but food should be avoided for several days The fluid content of the body can be kept up by the introduction of fluid in other ways if the swallowing of cool drinks is too painful An ice bag brings comfort when applied to the esophagus above the thorax

As stenosis of the esophagus even up to complete stricture may result from acute inflammations it is important as soon as the acute phase has subsided to be prepared to dilate the esophagus should difficulty in swallowing develop These stenosing bands are often called webs If difficulty in swallowing should develop it usually begins between the fourth and sixth weeks A silk thread should be swallowed and dilatation carried out by instruments passed along the thread If appreciable stenosis has developed the dilatation will probably have to be carried out for two years at regular intervals to be followed for two or three years more by an occasional check up Should rupture of the esophagus occur during dilatation the results are not necessarily fatal and experience suggests that conservative treatment may be as satisfactory as immediate surgery

In neglected cases in which the obstruction is complete so that a silk thread cannot pass the stricture it may be necessary to resort to retrograde dilatation after gastrostomy A gradually stenosing esophagus should never be allowed to reach the stage where a silk thread will not pass into the stomach

Ulcers —In bedridden or uremic patients ulcers sometimes occur in the esophagus They may also result from external pressure upon the esophagus These ulcers are of little clinical importance because their symptoms are usually overshadowed by the symptoms of the accompanying disease Ulcers similar to peptic ulcers occur in the esophagus They may develop in misplaced bits of gastric mucosa present in the esophagus They may cause no symptoms of importance or they may produce pain or difficulty in swallowing and even regurgitation of food

The pain should not be confused with angina pectoris Such an ulcer may perforate or bleed and the hemorrhage be severe An ulcer in a diaphragmatic gastric hernia occasionally simulates an esophageal ulcer

Diagnosis without the use of the esophagoscope may be difficult when the x ray does not reveal the ulcer The *treatment* of such an ulcer is similar to that of a peptic ulcer in the stomach Local applications may be made through the esophagoscope but their value is doubtful

Spasm—Spasm of the esophagus with pain or difficulty in swallowing must be differentiated from hysterical manifestations such as *globus hystericus* and functional pain without difficulty in swallowing The spasm may be (1) diffuse or localized at the lower end of the esophagus (cardiospasm) or (2) at the upper end and be associated with enlargement of the spleen secondary anemia and glossitis (Plummer-Vinson syndrome)

Diffuse spasm of the esophagus or cardiospasm may be painless and present only the symptom of difficulty in swallowing In other cases the substernal pain may be severe enough to simulate angina pectoris There is some question as to whether an attack of angina pectoris can be brought on by spasm of the esophagus or whether spasm of the esophagus may be induced by an attack of angina pectoris The two however may be associated Spasm of the esophagus can be brought on by worry but not by muscular exertion and it is not relieved by nitroglycerin Such attacks may be associated with gallbladder disease The electrocardiogram will not be influenced by spasm of the esophagus X ray studies show obstruction to swallowing during the attack of spasm Difficulty in swallowing due to obstruction from something outside the esophagus such as an aneurysm must be ruled out The *treatment* for diffuse spasm of the esophagus consists in attention to the patient's general condition and the usual procedure for handling some one who is under a nervous strain or is emotionally unstable

Cardiospasm—Whether cardiospasm is due to abnormal spasm of the muscle fibers of the esophagus or failure of normal muscular contraction to relax is still a disputed question If it is persistent there may result tremendous dilatation of the esophagus and hypertrophy of the walls A case is reported in which a dilated and hypertrophied esophagus herniated into the abdominal cavity Cardiospasm should be differentiated from an organic lesion due to growth or stricture and usually this can be done by x ray study but occasionally an esophagoscopic examination is necessary Spasm may be superimposed upon an organic lesion Dilatation of the spastic area by an instrument passed along a previously swallowed silk thread is the usual method of treatment. This may be done without an anesthetic and often one dilatation will suffice Sometimes the cardiospasm will return after several years The patient s general condition and environment must be considered in regard to causes for reflex spasm

Plummer Vinson syndrome sometimes called hysterical dysphagia usually occurs in women more than forty years of age is more common among Scandinavians and inhabitants of the British Isles and is rare in Hebrews In addition to the evidence of an unstable nervous system there is hypochromic anemia enlargement of the spleen, and glossitis In these cases the obstruction is at the upper end of the esophagus and responds to dilatation with sounds Even the passage of a small sound without dilating the esophagus often results in complete cure. Recurrence may call for subsequent dilatation As the anemia and difficulty in swallowing disappear, the soreness in the mouth clears up and the spleen diminishes in size

Tumors—Both malignant and benign tumors of the esophagus occur Carcinoma is the most common type Sarcoma is rare Fibromas papillomas hemangiomas lipomas and accessory thyroid tumors have been observed in the esophagus and also diffuse fibromyomata involving practically the entire musculature of the tube Cysts may develop in the wall of the esophagus Benign tumors may become large enough to cause obstruction or they may become pedunculated and even protrude from the mouth.

Carcinoma—This tumor is more common in men than in women It is usually situated at one of the three natural narrowings of the esophagus (1) at its upper origin (2) at the point where the left bronchus crosses in

front of it, or (3) at the point where it passes through the diaphragm The last is the commonest site

SYMPTOMS —Increasing difficulty in swal lowing usually without pain is the most frequent initial symptom Pain in the epi gastrium is a fairly common initial symptom and loss of appetite or belching of gas and hiccoughs have been reported to be the first symptoms noted As the disea e progresses signs of starvation gradually develop The patient loses weight rapidly and constipa tion becomes prominent because of the small amount of food absorbed Thirst is very dis tressing if the obstruction is complete Hem orrhage may occur if ulceration is present The blood may appear in the vomitus or only as tarry stools

DIAGNOSIS —The x ray examination usu ally establishes the diagnosis but it should be confirmed by esophagoscopic examina tion and biopsy

TREATMENT.—Recent advances in at tempts to remove malignant growths from the esophagus and in the establishment of an artificial esophagus are encouraging enough to stimulate the clinician to diag nose these cases early and refer them to a surgeon If surgery is contraindicated the growth may be retarded by deep x ray ther apy If the obstruction is pronounced grad ual dilatation may give temporary benefit Feedings by rectum or through a gastros tomy opening are on the whole unsatisfac tory If thirst is present fluids should be in troduced by rectum under the skin or in the veins Opiates should be liberally employed as the disease progresses

Esophageal Varices —Dilatation of the veins at the lower end of the esophagus is common if there is any obstruction to the return of blood either through the inferior or superior vena cava or through the portal circulation because the veins of the esoph agus connect with all three and anastomose with each other The most common cause of dilatation of the veins of the esophagus is cirrhosis of the liver It may occur in dis ease of the spleen with a normal liver The dilated veins may not produce any symp- toms or they may rupture and cause a sud den unexpected hemorrhage Attempts to decide upon the cause of the unexpected hematemesis should not be made until the bleeding has entirely ceased and then blind instrumentation should be avoided If the x ray study fails to show the varices exam ination with esophagoscope is indicated

There is no specific *treatment* for dilated veins in the esophagus

Rupture —Rupture may occur in a nor mal or diseased esophagus Rupture in a normal esophagus has been reported as caused by persistent vomiting wounds of foreign bodies or from heavy lifting Forced swallowing in a diseased esophagus may cause rupture or the natural progress of the disease may produce it The rupture of a diseased esophagus may extend into the respiratory tract and produce a fistula Al though there has been some success in the surgical treatment of rupture it should be remembered that recovery has been reported without surgical interference The *diagnosis* is readily made by x ray study as it will show the barium passing outside the lumen of the esophagus

Foreign Bodies —A foreign body may lodge in the esophagus without producing symptoms or may produce symptoms of obstruction very rapidly In children in ad dition to the difficulty in swallowing there may be definite interference with respiration The x ray may demonstrate the foreign body either directly when it casts a direct shadow or by a defect in the barium shadow if the foreign body does not cast a shadow Occasionally the foreign body is revealed by the barium which adheres to it after the remainder of the barium has reached the stomach

A foreign body should be removed with the aid of the esophagoscope as soon as the diagnosis is made Attempts to push a for eign body into the stomach or the blind re- moval of a foreign body from the esophagus without preliminary inspection are both dan gerous procedures

CHANNING FROTHINGHAM

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DISEASES OF THE STOMACH

Anatomic Variations—The shape and position of the stomach depend upon the constitutional type of the individual, upon his adiposity, and upon the condition of his anterior abdominal musculature In the relatively short, thick sthenic person with tense abdominal wall the stomach lies high in the left upper abdomen and is "steer horn" in shape whereas in the long, lean thin individual, the greater curvature is likely to extend to the brim of the true pelvis in the shape of the letter "J" This condition is often called gastroptosis and a symptomatology erroneously ascribed to it The important consideration is not *where* the stomach is but *how* it functions and such stomachs do function satisfactorily The vague digestive symptoms and disturbances often seen in these patients are not due to the location or position of the stomach

WALTER L PALMER

CONGENITAL ANOMALIES

THE three important congenital anomalies of the stomach are hypertrophic stenosis of the pylorus diverticula and diaphragmatic herniation, including the so called "thoracic stomach" with a short esophagus

HYPERTROPHIC STENOSIS OF THE PYLORUS

Definition—Hypertrophic stenosis of the pylorus consists of an obstructive narrowing of the pylorus accompanied by and apparently due to hypertrophy of the pyloric muscle

In Infants—Hypertrophic stenosis is found most frequently in infants two or three weeks old although it may occur at any time between the ages of ten days and three or four months The condition is three or four times more common in males than in females It is generally attributed to congenital hypertrophy with or without spasm At operation or autopsy the pylorus is found to consist of an oval tumor of muscular tissue 2 to 3 cm long and 1 to 2 cm in width hard, at times almost cartilaginous in consistency, and with no histologic evidence of inflammation However patients are occasionally seen with the typical clinical syndrome in whom at operation no hypertrophy is found, the obstruction presumably being due therefore, to spasm

Symptoms and Diagnosis—The symptoms are projectile vomiting constipation or obstipation decreased urinary output and rapid loss of weight Bile is rarely present in the gastric content On physical examination the most characteristic feature is the demonstration of large peristaltic waves passing from left to right across a distended globular stomach which fills the upper abdomen after eating If the child is relaxed adequately a tumor resembling a small peanut or marble may be palpated frequently, deep in the abdomen at the outer border of the right rectus muscle a few centimeters below or immediately under the costal border The diagnosis of pyloric obstruction is confirmed by roentgenologic examination When the factor of *spasm* predominates a somewhat milder picture is seen The vomiting tends to be explosive rather than projectile the peristaltic waves are less marked and a tumor is not palpated The stools may be scanty and may be soft rather than hard in consistency These cases outnumber those of true hypertrophic stenosis of the pylorus by about 30 1 and usually respond well to medical treatment

Treatment—In both types, medical treatment should be tried first provided the condition of the infant warrants it Sodium phenobarbital ⅛ grain given immediately before each feeding is very effective more so than atropine but it may be combined with atropine 1/1000 grain Atropine alone in large doses is undesirable because it may produce distention of the bowel dryness of the nose and throat and cerebral stimulation The diet should consist preferably of breast milk or a prepared milk giving a fine curd Thick cereal feeding may be used The infant should be watched most carefully

If a definite and favorable response is not secured within a few days or if the symptoms grow worse with dehydration and fever operation should be performed at once When a tumor is palpable operation is, as a rule required and it may become necessary in cases in which a tumor is not palpable The surgical procedure known as the

Rammstedt operation and consisting of a longitudinal incision through the pyloric muscle down to the mucosa ranks among the most successful ones in the field of abdominal surgery and has a mortality rate in competent hands ranging from 2 to 6 per cent

In Adults —Hypertrophy of the pylorus is seen in adults with and without stenosis and with and without symptoms The congenital origin of the hypertrophy has been questioned It has been noted however that periodic attacks of nausea and vomiting are less frequent throughout childhood and later adult life in patients operated on in infancy for hypertrophic stenosis than in those treated medically Cases of periodic nausea and vomiting have been described beginning in childhood and continuing until old age in which the pylorus was found to be markedly hypertrophied by the development of massive muscular bundles apparently congenital in origin On the other hand in the adult pyloric hypertrophy is often associated with some acquired gastric diseases such as gastric ulcer or gastritis Some authors ascribe hypertrophy of the pylorus to extragastric lesions such as cholelithiasis and chronic appendicitis but there is little evidence to support such a view

Symptoms and Diagnosis —The primary symptom is vomiting with or without pain The pain is usually due to an associated lesion such as gastric ulcer for pyloric obstruction *per se* does not produce pain The diagnosis of hypertrophic stenosis in the adult cannot or should not be made on clinical evidence alone Roentgenologically it may be evident from dilatation of the stomach the abnormal width of the pylorus and the crescentic indentation of the base of the bulb although in some normal individuals the pylorus is quite wide and a crescentic indentation may be made out in the base of the bulb An important and difficult task is the differentiation of benign and malignant hypertrophy of the pylorus the so called *carcinoma fibrosum* which usually begins in the pyloric end of the antrum The history in such cases is usually of short duration whereas in true hypertrophic stenosis it extends over many years Roentgenologic evidence of neoplasm may be found in an infiltration of the antrum and an absence of the crescentic indentation of the bulb In cases of pyloric hypertrophy associated with gastric ulcer or of gastric ulcer associated with pyloric hypertrophy the ulcer may produce little or no pain and be unsuspected until demonstrated roentgenologically or gastroscopically

Treatment —Treatment depends upon the severity of the symptoms and upon the associated conditions present If the stenosis is not marked no treatment may be in order If gastric ulcer is present the usual ulcer management may be followed unless the pyloric obstruction interferes If any reasonable doubt exists as to the nature of the pyloric lesion operation should be seriously considered Exact differentiation is usually as difficult at the operating table as it is preoperatively and hence as a rule in such questionable cases if operation is undertaken subtotal gastrectomy should be performed In true hypertrophic stenosis pyloroplasty or simple gastro-enterostomy may be sufficient Atropine is of no value in the differentiation of the various types of pyloric hypertrophy or in their therapy

WALTER L PALMER

DIVERTICULA

Definition —A diverticulum is a pouch opening out from a tubular organ True diverticula contain all of the coats of the normal stomach and are either congenital or secondary to pulsion and traction false diverticula lack the muscular coats and are attributed to weakening of the gastric wall from local disease as in gastric ulcer

Incidence and Location —True diverticula of the stomach are rather uncommon false diverticula are quite rare Both types are encountered as a rule accidentally in the course of a routine x ray examination or at autopsy They are seen most frequently roentgenologically in the region of the cardia but any part of the stomach may be involved Duodenal diverticula are more common than gastric Congenital diverticula of the duodenum occur usually in the second and third portions whereas acquired diverticula develop almost exclusively in the first portion Practically all diverticula of the

duodenal bulb are secondary to duodenal ulcer

Symptoms—Gastric and duodenal diverticula rarely cause distress although occasional cases have been described in which a marked inflammation was found about the duodenal diverticulum and relief of epigastric distress obtained by the removal or *invagination of the diverticulum* The belching discomfort, or pain is usually to be attributed to the acompanying disease or to a functional disturbance independent of the diverticulum

Treatment—Direct treatment of the diverticulum is rarely indicated Concomitant diseases such as ulcer or carcinoma or concomitant functional disturbances should be treated appropriately Relief from the distress is usually obtained without directing attention to the diverticulum In rare cases surgical treatment with excision or invagination of the diverticulum may be required

WALTER L PALMER

DIAPHRAGMATIC HERNIA

Diaphragmatic hernia is discussed in the section on Diseases of the Diaphragm (p 886)

FOREIGN BODIES IN THE STOMACH

Description—The foreign bodies most frequently swallowed are those taken accidentally by children, such as pennies and marbles, which in time pass through the stomach and intestine without harm Sharp-pointed articles, such as needles pins, and especially open safety pins are likely to penetrate the wall of the intestine and lead to peritonitis or abscess formation In the insane, the stomach may be found to contain a most varied assortment of nails spoons forks knives and other objects which may remain for years without causing symptoms *Bezoars* are conglomerations of swallowed foreign material such as hair (trichobezoars) hair and vegetable fiber (trichophytobezoars) or vegetable fiber alone (phytobezoar), usually due to persimmons *Hair balls* are the most frequent and are found in women addicted to the habit of chewing the ends of their hair *Gastroliths* have been reported from the long continued use of calcium or magnesium powders Spontaneous cholecystogastric fistula formation may lead to the extrusion of *gall stones* into the stomach

Symptoms—Foreign bodies in the stomach rarely cause symptoms unless there is an associated ulcer or gastritis

Treatment—Treatment is indicated only when definite distress is present or when the foreign body constitutes a real menace as in the case of a needle or an open safety pin The procedure indicated is usually surgical removal by means of laparotomy, for this is on the whole less dangerous simpler and more effective than open tube gastroscopy

WALTER L PALMER

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DISTURBANCES OF GASTRIC FUNCTION

SENSORY DISTURBANCES

Hunger and Appetite—Hunger and appetite were interpreted by Beaumont and subsequent workers as sensations differing only in degree but Cannon and later Carlson, very carefully differentiated the pleasant sensation of appetite related to previous sensations of the smell and taste of food from the disagreeable and painful sensation of hunger the essential factor of which the epigastric hunger pang was shown to be produced by contractions of the empty stomach The average individual in fasting does not distinguish sharply between hunger and appetite for the accentuation of the appetite is interpreted merely as a portion of the *total complex of hunger*, which may be divided into the following components

(*A*) Sensory

1 Pleasant olfactory and gustatory sensations with their associated pleasant memories of the taste and smell of food constituting appetite

2 Painful 'hunger pangs resulting from contractions of the empty stomach or intestines

3 An indefinite unpleasant generalized steady and continuous sensation interpreted as hunger and vaguely referred to the abdomen
4 Accessory phenomena such as lassitude weakness drowsiness faintness irritability restlessness and headache

(B) Associative or Imaginative The mind associates these various sensations with indefinite concepts of food or with definite images of specific foods

The phenomenon of hunger is thus seen to be a complicated sensory and associative process consisting of an accentuation of the pleasant sensation of appetite and the various unpleasant sensations of hunger including the painful contractions of the empty stomach and all associated with definite or indefinite concepts or imageries of food

Excessive appetite and *hunger* occur in various conditions such as in convalescence from an acute infectious disease like typhoid fever The digestive tract is then able to digest and absorb unusual amounts of food in order to restore rapidly the weight lost earlier A similar condition may obtain in thyrotoxicosis in which the requirement of food is maintained at a high level because of the excessive metabolism In diabetes mellitus the glucose in the blood is not available to the tissues and hunger and polyphagia result In peptic ulcer the distress is often interpreted as hunger because the patient fails to differentiate it from a hunger pang or because it occurs when the stomach is thought to be empty and is relieved by food taking The epigastric pang of hunger and the pain of peptic ulcer arise in the same organ and have in part but in small part only the same mechanism

Bulimia a term applied to an inordinate appetite and food intake is a purely psychologic phenomenon Continued excessive hunger and its resultant excessive ingestion of food lead eventually to obesity except in diabetes mellitus or thyrotoxicosis

Loss of appetite and of *hunger* is a variable but common symptom in disease of all kinds When it appears suddenly in individuals known to have been in good health it is a highly important symptom and warrants a most thorough search for the cause It is an early and prominent symptom in many cases of gastric or pancreatic neoplasm Therapeutically the primary indication is that of the underlying disease Liver and liver extract are curative in the anorexia of pernicious anemia In other deficiency states such as beriberi and pellagra the administration of brewers yeast or of thiamine chloride or of nicotinic acid results rather dramatically in improved appetite and increased food consumption Multiple vitamin deficiencies are probably more frequent than has been recognized generally and are relieved by proper therapy but nevertheless vitamins cannot be relied upon as a universal cure for loss of the desire for food Stimulation of the appetite itself is largely a psychologic problem Good food served attractively and with a cheerful smile is essential Stomachics are of suggestive value only Alcoholic beverages may be helpful if given with adequate suggestion but care must be exercised lest a neurotic individual take advantage of the opportunity afforded to become a chronic alcoholic Insulin seems to increase appetite hunger and food consumption in certain individuals but it too is of greatest value if given with strong suggestion

Anorexia Nervosa —*Definition* —Anorexia nervosa first clearly described by Sir William Gull in 1868 is a syndrome consisting of emaciation scaphoid appearance of the abdomen and amenorrhea It occurs chiefly in young girls but except for the amenorrhea the essential features of the syndrome are seen in both sexes and in almost all age groups Gull considered the condition to be due to a psychic loss of appetite resulting from a morbid mental state and so named it anorexia nervosa'

Symptoms and Diagnosis —Loss of appetite is the outstanding feature of the disorder and yet one about which the patient rarely complains The emaciation may be extreme progressing even to the point of nutritional edema The tissue of the breast is said to be preserved but it is often very scant A striking characteristic noted by Gull and subsequent observers is the wilfulness and remarkable energy of these patients which is in strange contrast to their prematurely senile or cachectic appearance

The basal metabolic rate may be markedly lowered The glucose tolerance curve is, as a rule, low or indeed almost a straight line, indicating presumably a delayed intestinal absorption, for the curve is normal when the glucose is given intravenously After recovery from the inanition the curve becomes normal The axillary and pubic hair are usually well preserved may become sparse but are almost never absent a point perhaps of value in differentiating the condition from Simmonds' disease in which such loss of hair is considered rather characteristic Careful inquiry will usually disclose *some precipitating nervous or emotional* cause The patient may have considered herself overweight, started to reduce and continued the procedure or she may have taken this means to express a parental conflict or her disappointment in love Skilful management usually leads to recovery but death *may ensue Considered from the psychiatric* point of view the mental patterns of anorexia nervosa are not uniform Most of them are psychoneuroses or depressions of various kinds, but in some cases, the picture approaches the true psychosis

Treatment — Superficial psychotherapy with encouragement and friendly interest perhaps conveyed with tonics and stomachics may suffice in the milder cases Often, however a temporary or even a permanent change of environment is essential The mode of living or the "life situation' may need readjustment Formal psychiatric care including psycho analysis may be indicated Success is usually achieved with some one of these measures but occasionally *all of them fail Thyroid extract* is not indicated for the low metabolic rate for this returns to a fairly normal level once satisfactory nutrition and consumption of food are achieved The low metabolism is a manifestation of *starvation rather than* primary hypothyroidism

Simmonds' Disease —*Definition* —Simmonds disease described by Simmonds in 1914 is a similar syndrome attributed to destruction of the anterior *lobe of the pituitary* gland

Symptoms and Diagnosis —It is difficult if not impossible, to distinguish clinically the syndrome of Simmonds' disease from that of anorexia nervosa Typically *the patient with* Simmonds' disease is a parous woman past forty years of age The symptoms are emaciation *premature aging* gonadal atrophy amenorrhea, loss of libido dental caries and loss of teeth microsplanchnia marked depression of the metabolic rate loss of hair from the axillae, pubes and scalp, and various abnormal mental reactions The apathy is often contrasted with the remarkable energy seen in anorexia nervosa Symptoms such as these are all known to result from continued loss of appetite and chronic inanition The question arises whether Simmonds' disease is an advanced and chronic form *of anorexia* nervosa with secondary changes in the pituitary gland or whether anorexia nervosa is to be attributed to a functional disturbance of the pituitary, or whether the two conditions are independent of each other Cases of the Simmonds syndrome have been de*scribed with and without* definite disease of the pituitary at autopsy Anterior pituitary disease occurs without the Simmonds syndrome Experimentally emaciation and cachexia may follow extirpation of the pituitary or be produced *by chronic* inanition in which case glandular changes are present

Treatment —The therapeutic value of specific or nonspecific glandular therapy has not been proved although in many instances improvement has followed the *use of such* measures and has therefore been ascribed to them Regardless of the relationship ultimately found to exist between Simmonds disease and anorexia nervosa the therapeutic indications are the same in *both* and are symptomatic and psychotherapeutic in *nature In extreme* cases feeding through a nasal catheter or the parenteral administration of fluid may be necessary for a few days or weeks

Nervous Vomiting —Nervous vomiting *is strictly speaking* neither a sensory nor a motor disturbance of the stomach but it may be briefly considered here because it is a manifestation of a basic psychiatric problem similar to anorexia nervosa It is in *some respects more* dramatic but less subtle than anorexia and more typically hysterical in nature although the patient usually does not appear to be hysterical The *most* characteristic feature is the continued effortless *vomiting of meals* usually immediately after

eating with no loss of weight The patient complains bitterly but looks well Gastric and esophageal disease particularly cardio spasm should be excluded The therapy is a psychiatric problem Sedatives are valuable Fluids should be administered parenterally for a few days until the acute phase has passed The chronic forms of nervous vomiting may be very resistant to treatment

Migraine —Migraine is not a disease or a primary disorder of the stomach The nausea and vomiting are primarily psychogenic or at least central in origin So-called abdominal migraine is abdominal only in that abdominal symptoms particularly nausea and vomiting are present and dominate the clinical picture The headache is the essential although often not the outstanding feature of the syndrome and gives the clue to the diagnosis

WALTER L PALMER

MOTOR DISTURBANCES

Gastric atony is not a clinical entity The large sagging stomachs of gastroptosis may empty slowly but they are not abnormal and do not give rise to symptoms In pyloric obstruction the stomach is dilated but not atonic

Hyperperistalsis and hypertonicity of the stomach are likewise not disease entities or the basis for symptoms They are often found in tense nervous individuals in patients with duodenal ulcer in the presence of complete achlorhydria and occasionally in gastric carcinoma In diabetes mellitus the contractions of the empty stomach may be increased and lead to inordinate hunger

Spasm of the entire stomach or of a segment of the stomach has been described in tabes dorsalis in other lesions of the central nervous system and also in the presence of extragastric abdominal conditions such as cholelithiasis or pancreatic disease The relationship of such spasm to abdominal pain is questionable for the pain of tabetic gastric crises seems not to arise in the stomach itself and segmental gastrospasm has been observed without pain On the other hand painful gastric spasm has been noted in the normal stomach Localized muscular spasm is not infrequently seen with gastric lesions as in hour glass contracture associated with benign ulcer, the contracture disappearing when the ulcer heals Painless spasm of the pylorus as evidenced by rather persistent closure occurs frequently with intrapyloric peptic ulcer and also with gastric and duodenal lesions adjacent to the pylorus Gastric ulcers several centimeters proximal to the pylorus on the lesser curvature are occasionally associated with a disturbance in the opening of the sphincter, presumably a reflex pylorospasm Contractions of the pylorus and of the stomach are on the whole independent of the sensation of pain but may be painful if sufficiently intense or if they occur in the region of an ulcer

Acute Dilatation of the Stomach —*Definition* —Acute dilatation of the stomach or acute gastromesenteric ileus is as the name implies a condition in which the stomach is extremely dilated flabby inactive and contains 1500 to 4000 cc of thin slightly colored gastric and intestinal liquid content The condition occurs chiefly as a postoperative or postpartum complication and is due to compression of the third portion of the duodenum between the spine and aorta posteriorly and the mesenteric root anteriorly Gastric dilatation is in part secondary to the obstruction and in part induced by the depression in gastric tonus resulting from the general anesthesia It is quite possible that the depression in gastric tonus precedes rather than follows the obstruction Another important factor may be the maintenance of the dorsal position for relief occasionally follows a change in position

Symptoms —The symptoms are variable and apparently result from distention of the stomach the loss of water and electrolytes and toxemia of indefinite origin The onset often is insidious the symptoms not marked and the severity of the condition not appreciated Pain is often slight or absent The more important symptoms are listlessness apathy lack of appetite epigastric fulness regurgitation nausea and vomiting The vomitus is usually dark brown green or black in color as a rule very foul smelling and copious consisting of large quantities of gastric biliary and pancreatic secretions The abdomen is soft distended without visible peristaltic waves and gives a succussion splash The urine is scant As the con

dition progresses the signs of shock or collapse appear, a cold clammy skin, anxious facies, rapid pulse, low blood pressure, shallow, quick respirations and delirium, followed by coma and death

Treatment —Treatment consists of gastric lavage, the administration of large amounts of fluid parenterally, and frequent changes in position In the modern hospital, the routine postoperative use of the Wangensteen continuous *suction apparatus* has proved most effective In some cases the suction must be continued for several days but if the parenteral replacement of fluids is adequate, usually 2 to 4 liters per twenty four hours recovery occurs

WALTER I PALMER

SECRETORY DISTURBANCES

Normal and Abnormal Variations in Gastric Secretion —Pathologic alterations in gastric secretion apparently occur exclusively in the direction of depression in total volume or in concentration or both The normal stomach secretes gastric juice *as acid as that in disease and as far as* is known in as large an amount although there is some evidence that in many cases of ulcer particularly those associated with stenosis the night secretion of acid gastric juice is greater than that usually seen in normal individuals Variations in gastric secretion are not directly correlated with gross or microscopic changes in the gastric mucosa Normal individuals with essentially normal mucosae, gastroscopically exhibit a wide variety of responses to histamine ranging from complete achlorhydria with a *p*H value of 8 7 to a highly acid juice with a hydrogen ion concentration of 0 1 normal (*p*H 1 0) These differing secretory rates are not to be correlated definitely with specific symptoms or diseases except for the fact that chronic peptic ulcer does not occur in the continued absence of acid gastric juice nor does pernicious anemia or combined column degeneration of the spinal cord occur in its presence

Achlorhydria —*Occurrence* —The complete absence of all gastric juice *achylia gastrica* is rarely seen for some secretion containing *ferments* in small amounts is almost always present. The more exact terms *achlorhydria* and *anacidity* are preferable Complete achlorhydria as shown by the absence of acid in the gastric secretion even after the subcutaneous injection of histamine hydrochloride, so called histamine proved achlorhydria occurs in approximately 10 per cent of all individuals, in about 60 per cent of patients with gastric carcinoma in about 85 per cent of cases of gastric lues in nearly *all cases of adenomatous polyps or gastric* polyposis, and in all patients with pernicious anemia or combined cord degeneration

Etiology —The anacidity is usually ascribed to atrophic gastritis because such mucosal changes are found histologically in pernicious anemia It has been observed however that in many cases of anacidity with gastric carcinoma the mucosa is not atrophic histologically and no pathologic changes are evident to account for the achlorhydria Similarly in many cases of histamine proved anacidity in apparently normal individuals the mucosa as seen gastroscopically is essentially normal or shows evidence of relatively slight or patchy inflammation On the other hand extensive *atrophy of the gastric mucosa* undoubtedly leads to a depression or suppression of gastric secretion although surprising degrees of atrophy may be seen gastroscopically in stomachs found to secrete acid gastric juic

Symptoms —Achlorhydria *per se* is not important clinically It does not produce gastric symptoms From the standpoint of digestion it is also not particularly important for intestinal digestion almost *completely* compensates for the absence of gastric digestion The stomach empties somewhat more rapidly in achlorhydria than it does *when acid is present*, but this process is not affected by the oral administration of acid The term *gastrogenous diarrhea* referring to diarrhea with achlorhydria is not appropriate for there is no satisfactory proof that the diarrhea is related *to the achlorhydria* The functional diarrheas seen in patients with achlorhydria do not differ in their symptomatology or in their response *to dietary management* from those seen in individuals with acid gastric secretion

Treatment —The time-honored therapy is dilute hydrochloric acid given in doses of 1 to 4 cc in a half to a whole glass of water

before each meal The results are often strik ing but similar results may be obtained without the use of acid suggesting that the real role of the acid is that of a psycho therapeutic agent The amount of acid ac tually given is too small to alter materially the hydrogen ion concentration of the gas tric or intestinal content

WALTER L PALMER

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NONSPECIFIC INFLAMMATION OF THE STOMACH

Definition—The term gastritis is usu ally applied only to acute or chronic non specific inflammations of the gastric mucous membrane although strictly speaking specific *lesions such as syphilis tuberculosis* and actinomycosis should be included

Morbid Anatomy—Acute and chronic inflammation is the most frequent pathologic process of the stomach Interstitial cellular infiltrations with collections of lymphocytes are almost invariably found in the wall of the stomach at autopsy More marked al terations such as hemorrhage in the super ficial layers of the mucosa erosion of the papillae and infiltration of the submucosa muscularis and serosa with lymphocytes plasma cells and polymorphonuclear leuko cytes are frequently observed Chronicity is evidenced by fibrous tissue proliferation in the gastric wall atrophy of the mucosa dis tortion or disappearance of the glandular structure and transformation of the normal glandular epithelium into the intestinal type with numerous goblet cells

WALTER L PALMER

ACUTE GASTRITIS

Description—Acute gastritis was orig inally and beautifully described in 1833 by William Beaumont who studied the mu cosa of the stomach of his servant Alexis St Martin through the fistula produced by a gunshot wound There are sometimes found on the internal coat of the stomach eruptions *or deep red pimples* not numer ous but distributed here and there upon the villous membrane rising above the sur face of the mucous coat. These are at first sharp pointed and red but frequently be come filled with white purulent matter At other times irregular circumscribed red patches varying in size or extent, from half an inch to an inch and a half in circum ference are found on the internal coat These appear to be the effect of congestion in the minute blood vessels of the stomach There are also seen at times small aphthous crusts in connection with these red patches Abrasions of the lining membrane like the rolling up of the mucous coat into small shreds or strings leaving the papillae bare for an indefinite space is not an uncommon appearance These changes came often lasted one day or more and disappeared

Etiology—With regard to etiology Beau mont states that After excessive eating or *drinking chymification is retarded* and although the appetite be not always im paired at first the fluids becomes acrid and sharp excoriating the edges of the aperture and almost invariably produce aphthous patches and the other indications of a dis eased state of the internal membrane

Symptoms—Beaumont s word again is authoritative These morbid changes and conditions are however seldom indicated

by any ordinary symptoms or particular sensations described or complained of, unless when in considerable excess, or when there have been corresponding symptoms of a general affection of the system They could not in fact, in most cases, have been anticipated from any external symptoms, and their existence was only ascertained by actual ocular demonstration

'It is interesting to observe to what extent the stomach, perhaps the most important organ of the animal system, may become diseased without manifesting any external symptoms of such disease or any evident signs of functional aberration Vitiated secretions may also take place, and continue for some time, without affecting the health in any *sensible* degree' In the century since Beaumont, these observations on the signs and symptoms of acute gastritis have been repeatedly confirmed Perhaps greater emphasis should be given to the incidence of such changes as seen pathologically in the course of all types of acute infectious disease However in spite of its frequency acute gastritis is probably of little clinical significance except as it may relate to chronic gastritis and its sequelae

Treatment—The treatment as implied by Beaumont, is that of abstinence from dietary indiscretions or perhaps indeed temporarily from all food Healing of the lesions and a return to a normal mucosa invariably occurs within a few days

WALTER L PALMER

ALCOHOLIC GASTRITIS

So called alcoholic gastritis is frequently diagnosed clinically on the basis of the clinical syndrome of nausea and vomiting after the ingestion of alcoholic beverages After a drinking bout the vomiting may be so persistent that the patient is unable to retain food or drink of any kind for several days The vomitus usually contains bile considerable amounts of mucus occasional flecks of blood and not infrequently streaks or even larger amounts of blood Hirsch in a histologic study of the stomachs of thirteen alcoholic addicts nine of whom had died of delirium tremens found no evidence of an acute or chronic inflammation Schindler and Gray, in a gastroscopic study of 100 men who had consumed an average of 2⅘ pints of alcohol daily for more than twenty years found the stomach to be normal in fifty five. The morning nausea is very difficult to explain It occurs as frequently when the stomach is normal as when it is diseased The symptoms are more likely to appear if the first swallow taken is water than if it is alcohol After two or three drinks of alcohol the nausea and vomiting usually disappear and do not recur until the following morning

WALTER L PALMER

CHRONIC GASTRITIS

Pathologic features of chronic gastritis cannot be directly or precisely correlated with clinical syndromes Indeed the diagnosis of chronic gastritis should be made only on the basis of anatomic evidence obtained at autopsy or laparotomy, or by gastroscopy The correlation between the pathologic and gastroscopic methods of study is fairly good Gastroscopically Schindler recognizes superficial atrophic and hypertrophic types of chronic gastritis

Superficial Gastritis—This condition is characterized gastroscopically by (1) reddening of the mucous membrane, (2) edema and (3) exudation The mucosa is friable small purpuric spots are common and small erosions are not infrequent The terms hemorrhagic erosive or ulcerative may be used in addition to superficial to describe the various features present The symptomatology if any of chronic superficial gastritis is still debatable for no one has succeeded in establishing a *definite gastritic* syndrome The condition is not infrequently seen gastroscopically in patients without gastric symptoms at the time of the examination it is rarely to be interpreted as the cause of distress The etiology is unknown and no treatment is indicated although numerous therapeutic programs have been advocated

Atrophic Gastritis—*Description*—The characteristic gastroscopic features are (1) the gray or greenish gray color due to the thinning of the mucosa in sharp contrast to the orange-red color of the normal stomach and (2) the presence of branching blood vessels seen through the thin mucosa Hemor

rhage into the mucosa is more frequent in this type of gastritis than in the others while erosions are less frequent The atrophy is usually rather localized and patchy in distribution but the entire mucosa may be involved

Relation to Other Diseases —In pernicious anemia during the phase of relapse the entire mucosa is invariably atrophic but marked improvement occurs following treatment with liver extract The propriety of ascribing the atrophy of the gastric mucosa in this disease to gastritis is still debatable In certain cases of iron deficiency anemia the gastric mucosa is also atrophic and improves markedly in appearance following suitable therapy Schindler considers that atrophic gastritis is usually the end result of a continued superficial gastritis There is a great deal of evidence that atrophic gastritis is the precursor or common etiologic background of pernicious anemia gastric polyposis and gastric carcinoma (see Fig 62) Certainly an atrophic gastric mucosa is present in all cases of pernicious anemia and is frequently found in neoplastic changes of the mucosa Konjetzny has presented histologic evidence of the complete transition from atrophic gastritis to benign and malignant epithelial neoplasia Considered in this light atrophic gastritis would appear to be a very important disease

Symptoms —The symptoms if any are indefinite although anorexia heartburn and various dyspepsias have been ascribed to it

Treatment —There is no acceptable evidence that treatment is of value except in those cases associated with pernicious or iron-deficiency anemia Hydrochloric acid may be given but it is of psychotherapeutic value only The possibility of carcinomatous metaplasia may be used as an argument for therapy in atrophic gastritis but this is scarcely permissible until more is known with regard to the actual occurrence and incidence of such neoplasia and also the real value of any proposed therapeutic procedure

Hypertrophic Gastritis —*Description* — This condition is characterized gastroscopically by a velvety slightly swollen dull loose spongelike appearance of the mucosa usually with the formation of granular nodules and larger nodes as may be indicated by the commonly used adjectives granular 'nodular verrucose' and hemorrhagic' At times the polypoid nodes may be difficult to differentiate from true polyps and neoplastic infiltrations Erosions and small ulcerations are frequent and usually multiple The cause of hypertrophic gastritis is unknown

Symptoms —There is evidence both clinical and histologic that the erosive and ulcerative forms of gastritis particularly in the hypertrophic type may cause symptoms consisting not only of epigastric distress identical with that seen in peptic ulcer but also massive gastric hemorrhage

Treatment —In such cases the distress disappears following the administration of a bland diet or the institution of a therapeutic program such as that used in peptic ulcer a more or less conventional Sippy program but the gastroscopic evidence of hypertrophic gastritis usually persists Symptomatic relief, however is all that is required for it is not necessary to insist on disappearance of the lesion as is the case in peptic ulcer Gastric lavage with silver nitrate or other medicaments is not indicated Following intensive radiation therapy directed at the stomach hypertrophic gastritis disappears and rarely recurs but the condition is almost never severe enough in itself to justify such treatment

Gastritis of the Postoperative Stomach —This is not a separate type of gastritis but it deserves special mention because of its severity and because it consists of a combination of the superficial and hypertrophic forms with marked erosive and hemorrhagic features In some cases the indefinite symptoms of epigastric distress and discomfort seem definitely attributable to the severe gastritis present There is no specific therapy and hence the treatment must be symptomatic When definite erosions and ulcers are present the therapeutic problem is that of recurrent ulcer

Gastritis Simulating Carcinoma —This also is not a separate type of gastritis but it deserves special mention These rather rare cases present clinical roentgenologic gastroscopic and indeed pathologic difficulties The inflammation involves chiefly the antrum and is accompanied by polypoid or pseudopolypoid changes in the mucosa which may be interpreted as precarcinomatous

proliferations, as "gastritis not yet carcinomatous" The polypoid infiltrative process is very difficult to differentiate from infiltrative neoplasm and is best treated by subtotal gastrectomy

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SPECIFIC INFLAMMATION OF THE STOMACH

CORROSIVE GASTRITIS

THIS type of inflammation follows the ingestion of corrosives, particularly acids taken accidentally or with suicidal intent Perforation of the stomach and death may ensue or spontaneous recovery may occur Pyloric stenosis may result either from the acute inflammation or from the connective tissue proliferation and require surgical relief

WALTER L PALMER

PHLEGMONOUS GASTRITIS

This is an acute, infectious usually pyogenic inflammation of the stomach involving chiefly the submucosa It occurs as a rare complication of septicemia or other infectious processes as a rare surgical complication following operations on the stomach or other intra abdominal organs as a complication of peptic ulcer or more frequently of gastric carcinoma Focal abscesses of the mucosa and submucosa are not infrequently seen in the gastritis associated with gastric carcinoma but true phlegmonous gastritis is rare The symptoms consist of the sudden appearance of acute epigastric pain and fever often preceded by a chill with vomiting prostration a rapid weak pulse and rapid exitus The diagnosis is very rarely made antemortem In the pre sulfonamide era there was no specific or empiric treatment Now the sulfonamide should be used, although their value in this disease is not yet established

WALTER L PALMER

SCIRRHOUS OR SCLEROSING GASTRITIS

This lesion commonly called *leather bottle stomach* or *linitis plastica* is very rare The stomach is small contracted and rigid, due to a diffuse fibrous thickening of the submucosa It is customary to speak of two types benign and malignant The nature of the *benign* type is debatable Gastric syphilis may produce a diffuse fibrosis of the stomach Scirrhous *carcinoma* of the stomach is rather common and it is well recognized that in some cases of this type the tumor cells may be extremely difficult to demonstrate histologically The course may be very chronic It is quite probable that all cases of *linitis plastica* are luetic or neoplastic in origin and that a nonspecific benign type does not exist but conclusive proof is lacking The outstanding symptoms are moderate epigastric distress inability to eat more than a small meal, regurgitation belching and loss of weight (see Fig 65)

WALTER L PALMER

GASTRIC LUES

Incidence —Syphilis of the stomach is relatively rare but it occurs in all age groups and in both sexes although it is more frequent in males

Morbid Anatomy —As in all tertiary lues the characteristic pathologic lesion is the gumma Four different types are seen (1) The solitary ulcerated gumma (2) multiple ulcerated gummata forming a nodular serpiginous syphilid (3) diffuse nodular non ulcerated infiltration (4) chronic fibrosis The first type simulates benign gastric ulcer in appearance whereas the other three simulate carcinoma Histologically, perivascular round cell infiltration gummata obliterating endarteritis and phlebitis and with the appropriate technic *Treponema pallidum* may be demonstrated

Symptoms —The symptoms are variable

but epigastric pain or discomfort is the out standing feature The distress may simulate peptic ulcer but more often it suggests car cinoma in that it comes on immediately after eating and is accompanied by a marked loss of weight A mass may rarely be pal pable but massive hemorrhage and acute perforation almost never ocur Achlorhydria is present in about 85 per cent of the cases and gastric retention is noted in about a fourth

Diagnosis —The positive diagnosis of gastric syphilis is difficult The Wassermann test is almost always positive in the blood or spinal fluid or both Occult blood is not found in the stools Roentgenologically the lesion very rarely consists of a penetrating niche but usually suggests an infiltrative tumor The most frequent location is pre pyloric the defect concentric symmetrical and relatively smooth In some cases the middle of the stomach is involved in a dumbbell shaped deformity, the central con striction being as a rule long and tubular but occasionally forming a narrow hour glass In a small percentage of the cases the stomach is diffusely involved

Very few cases have been studied gastro scopically Schindler considers the demon stration of a brownish yellow very shallow large ulcer in a thickened gastritic area to be suggestive of syphilis

The problem of differential diagnosis arises almost exclusively in patients with a history or definite clinical evidence of lues including a positive serology Benign peptic ulcer and carcinoma are encountered in such patients much more frequently than is luetic involvement of the stomach

Treatment —A syphilitic gastric lesion should respond rapidly to antiluetic therapy If it does not and if occult blood is pres ent in the stool carcinoma is almost in variably present The diet is relatively un important The pyloric stenosis may be suf ficient to warrant gastro enterostomy

Walter L Palmer

TUBERCULOSIS OF THE STOMACH

This process is usually demonstrated at autopsy as an accidental finding in patients dying from pulmonary tuberculosis Clagett and Walters however found reports in the literature of 368 cases of clinically significant tuberculous gastric lesions of four pathologic types (1) the ulcerating type (2) the hypertrophic infiltrating type (3) acute miliary dissemination (4) extragastric lesions involving the stomach In at least 80 per cent of the cases the ulcerating type is the one found For some strange and un known reason about 10 per cent of the tu berculous lesions are associated with gastric carcinoma Clinically it is not possible to differentiate tuberculosis of the stomach from benign ulcer carcinoma or syphilis As yet the gastroscopic differentiation of tuberculous ulcers has not been made due perhaps to their rarity A positive diagnosis is established only by the demonstration of tubercle bacilli in the lesions Treatment is surgical resection of the involved portion being the operation of choice

Walter L Palmer

LYMPHOGRANULOMATOSIS

Hodgkin s disease may begin in the lymph oid tissue of the stomach and simulate car cinoma clinically roentgenologically and gastroscopically The diagnosis is usually made by the histologic examination of the resected specimen or of an excised lymph node

Walter L Palmer

RARE INFECTIONS OF THE STOMACH

Actinomycosis anthrax fungus infections nonspecific granulomatous ulcers diphther itic lesions and *agranulocytic ulcers* of the stomach are rare lesions seen at autopsy al most exclusively and hence they scarcely deserve clinical mention

Walter L Palmer

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GASTRIC NEOPLASMS

MESENCHYMAL TUMORS

Definition —Pathologically, gastric neoplasms may be divided into those of mesenchymal and those of epithelial origin but their clinical differentiation is difficult The mesenchymal tumors consist of fibromas myomas fibromyomas leiomyomas, myofibromas, hemangiomas, lipomas, angiomas dermoid cysts and the malignant sarcomas including the lymphoblastomas

Symptoms —Symptoms appear only when the tumor ulcerates bleeds obstructs the outlet of the stomach or becomes so large as to become noticeable to the patient as an abdominal mass The clinical picture is not characteristic There may be no symptoms Epigastric distress if present is usually not severe it may be induced by the taking of food relieved by food, or bear no relationship to food taking The symptoms and signs of anemia are often present

Diagnosis —Mesenchymal neoplasms occur in all age groups, but the finding of a gastric tumor in a patient in the first or second decade of life would be suggestive The roentgenologic demonstration of a circumscribed, apparently intramural nonulcerated mass would conform with the diagnosis of a relatively benign mesenchymal tumor such as a myoma or fibroma Gastroscopically such a diagnosis is indicated by the presence of intact mucosa overlying a smooth mass When ulceration is present the differentiation is more difficult if not impossible The roentgenologic and gastroscopic demonstration of marked mucosal infiltration with swollen distorted folds is very suggestive of lymphoblastoma but a similar picture may be produced by infiltrative carcinoma or hypertrophic gastritis The gastric analysis is not significant nor is the presence or absence of occult blood in the stool important except as it betokens the presence of a bleeding lesion

Treatment —The treatment indicated in all cases is operation with resection of the stomach and removal of the tumor if possible In the infiltrative sarcomas and blastomas resection is often not feasible but a biopsy either of the tumor itself or a metastatic lymph gland perhaps a cervical gland is valuable Lymphoblastomas and malignant mesenchymal tumors in general tend to be very radiosensitive and hence surprising results may be obtained with radiation therapy

WALTER L PALMER.

EPITHELIAL TUMORS

BENIGN MUCOSAL NEOPLASMS

Definition.—Benign epithelial or mucosal neoplasms include adenomas papillomas and adenomatous polyps of various kinds The distinction between benign and malignant new growths is of course a relative one for most benign tumors are potentially malignant and some malignant tumors are relatively benign The relationship of these lesions to atrophic gastritis pernicious anemia and carcinoma, will be discussed further in the section on carcinoma (see descriptive legend of Fig 62) Benign gastric polyps are uncommon although not rare Clinically the great difficulty lies in proving that they are indeed benign and not malignant In fact this difficulty is so great and the danger that even a benign polyp may undergo malignant change is so definite that surgical removal is as a rule indicated The pedunculated adenomas are usually benign whereas the broad based papillomas tend to be malignant but the distinction is not reliable

Symptoms —Pain is as a rule absent or slight and present only if the polyp prolapses into or through the pylorus or is sufficiently large to be caught and pulled by gastric peristalsis The usual symptoms are those of anemia resulting from continued bleeding

Diagnosis —The syndrome of pernicious anemia may be simulated even to the extent of a high color index with definite macrocytosis Achlorhydria is almost invariably present The diagnosis is made by the roentgenologic or gastroscopic demonstration of a polyp (Fig 61) Pernicious anemia and

gastric polyposis may coexist On the other hand the chronic bleeding may very rarely produce a blood picture simulating primary anemia or the blood loss may modify the hematologic picture of pernicious anemia if it is present The demonstration of combined cord degeneration speaks positively for primary anemia Occasionally decision as to whether the two diseases coexist must be deferred until the polyp has been removed and the subsequent course of the blood picture studied



Fig 61—Pedunculated gastric polyp in various phases of prolapse through the pylorus The patient, Unit No 116743 a woman forty four years of age had had indefinite abdominal distress intermittently for several years with occasional attacks of vomiting There was no anemia

Treatment —Treatment consists of surgical removal The polyp may be excised and the base cauterized or a subtotal gastrectomy may be performed The advantage of the latter procedure is that it protects the patient against carcinomatous change in the mucosa adjacent to the polyp The prognosis is excellent

WALTER L PALMER

CARCINOMA

Incidence —Cancer of the stomach kills more people than any other cancer of the body and therefore ranks high among the common causes of death There are approximately 27 000 annual deaths from gastric carcinoma in the United States constituting about 18 per cent of the total deaths from cancer The incidence of gastric carcinoma is increasing due apparently to the rapid lengthening of the life span which has occurred during the past fifty or seventy five years Gastric cancer is almost unknown in the first decade of life rare in the second uncommon in the third decade and common indeed thereafter from the age of thirty five on It occurs among all races of mankind in all parts of the world It is unrelated to occupation position in life social status contact with other patients or trauma Heredity may be important for families are not infrequently encountered in which the incidence of carcinoma in the stomach or in other organs is extremely high On the other hand gastric cancer is not infrequently observed in individuals with no *known* history of cancer in the family

Etiology —The cause of carcinoma is still unknown but the gradually accumulating evidence seems to show that cancer is not congenital that it does not develop from embryonal rests that it is not directly inherited although a predisposition to it may be inherited that it is an acquired disease and that it is neither infectious nor contagious Filtrable viruses and various chemical carcinogenic agents are under active investigation as potential causes of carcinoma Trauma is of etiologic importance only as far as it relates to the sequelae of corrosion of the mucosa as in acid or alkali poisoning or to the effect of the carcinogenic chemical agents Gastric ulcer is generally considered to be a precursor of carcinoma but the evidence is most inconclusive This problem is discussed in detail in the section on gastric ulcer

Konjetzny and numerous other investigators contend that gastric carcinoma never develops in a normal mucosa and that it results from chronic atrophic gastritis with hyperplasia The essential process is not the chronic inflammation but the regenerative



Fig 62—Polypoid intraluminal gastric carcinoma Note the subtraction type of filling defect of the lesser curvature This case (X—No 32830) illustrates the entire subject of the possible relationship between atrophic gastritis pernicious anemia gastric polypus and carcinoma The pati nt a male fifty-eight years of age developed pernicious anemia in April 1926 responded well to the oral administration of whole liver *throughout the summer of 1926* was operated on in November 1926 because of the roentgenologic demonstration of a gastric tumor A pedunculated polyp 6 × 4 × 3 5 cm was removed the base being cauterized Sections of the polyp disclosed adenocarcinoma but no tumor *cells* were found in the pedicle The patient continued well although he found it necessary to use whole liver liver extract by mouth and later liver extract intramuscularly In the spring of 1934 the patient noted unusual hunger occurring before meals and at bedtime relieved by food X ray disclosed the polypoid intraluminal mass shown above Type I (Borrmann) A subtotal gastrectomy was performed in June 1934 a large fungating mass being *found* on the greater curvature of the stomach Histologically the tumor was found to be an alveolar colloid carcinoma A nodule was present in the serosal surface of the stomach at the site of the tumor and hence radiation therapy was administered postoperatively *The need* for persistent parenteral liver therapy has continued but in all other essential respects the patient has remained in excellent health for the past nine years and has now reached the age of 75

change in the epithelium resulting from the chronic gastritis In Konjetzny s extensive experience gastric carcinoma is always associated with such changes The transitional stages from chronic atrophic gastritis with small areas of hyperplasia to papilloma and carcinoma have been clearly shown. There is abundant evidence to prove that *carcinoma does not begin with a single cell.* but that many cells throughout an area of variable size may undergo malignant neoplasia Striking illustrations of these facts are seen in cases of multiple polyposis and frank multicentric carcinoma Chronic atrophic gastritis bears a fundamental relationship *not only to gastric polyposis and* carcinoma but also to pernicious anemia as has already been mentioned It is not yet clear whether or not the incidence of gastric carcinoma in cases of pernicious anemia under treatment is greater than should be expected in the age groups under consideration nor is *the effect of liver or liver extract* upon the gastric mucosa sufficiently known or understood although it has been established that definite improvement in the appearance of the gastric mucosa may occur after its administration

Gastric carcinoma then is an acquired disease developing in a pathologic gastric mucosa and probably arising on the basis of cellular reaction to continued injury or inflammation perhaps due to a toxin or infection but more probably due to some specific chemical carcinogenic substance or group of substances

Morbid Anatomy—Carcinoma *may* develop in any part of the stomach although fortunately for therapy the majority occur in or involve primarily the distal half or third There are many types of gastric carcinoma but for practical purposes the old classification of Borrmann and other pathologists *is helpful Four macroscopic types* may be distinguished as follows

1 The polypoid mushroom sharply circumscribed growth developing chiefly into the lumen of the stomach (see Fig 62)

2 The ulcerated circumscribed dishlike tumor with clearly defined borders (see Fig 63)

3 The ulcerated carcinoma with a definite wall or a sharp border on one side only not sharply circumscribed and infiltrating the gastric wall (see Fig 64)

4 The diffuse infiltrating type perhaps ulcerated superficially without definitely palpable borders and often with thickening of the wall of the entire stomach *(see* Fig 65)

Metastases tend to develop later in groups 1 and 2 than in groups 3 and 4 as expressed in the pathologic dictum Large primary growth, few metastases small primary growth many metastases'

The extent and the character of the ulceration may be affected by the gastric juice When acid gastric juice is present the base of the carcinomatous ulcer appears cleanly digested rather than necrotic and its edge tends to be sharp rather than ragged and indefinite The ulceration may rarely extend beyond the carcinoma into normal tissue and thus produce a lesion grossly indistinguishable from a benign ulcer

The *microscopic types* of gastric carcinoma are variable and are not to be correlated with the macroscopic forms All grades of differentiation are seen from the highly differentiated cylindrical adenocarcinoma to the poorly differentiated or almost entirely undifferentiated cellular carcinomas resembling sarcomas Broders classifies the malignancy of tumors on the basis of the degree of differentiation present histologically into the following four grades

1 Carcinoma cells 75 to 100 per cent differentiated

2 Carcinoma cells 50 to 75 per cent differentiated

3 Carcinoma cells 25 to 50 per cent differentiated

4 Carcinoma cells 0 to 25 per cent differentiated

The tendency is for *metastatic lesions* to develop most rapidly in poorly differentiated tumors least rapidly in the highly differentiated ones The spread takes place by way of the lymphatics the peritoneum or the blood Presumably metastases would occur in all patients if they lived long enough but at the time of autopsy the incidence of metastases is 14 to 25 per cent The adjacent lymph glands are usually first involved Infiltration of the supraclavicular node the so called Virchow s node is found in approximately 5 per cent at autopsy Hepatic involvement peritoneal and omental metastases and direct extension into the esophagus are all quite common

The neoplasm rarely extends beyond the pylorus into the duodenum Any adjacent organ may be involved by direct extension, particularly the pancreas liver colon spleen or diaphragm Peritoneal spread to the ovaries the so called *Krukenberg tumor* invariably involving both ovaries, occurs in approximately 5 per cent of the cases Similar implantation metastases occur in the male in the rectal pouch the so called rectal shelf of Blumer Pulmonary metastases are less frequent than might be expected Other rather rare but nevertheless definite sites of metastases are the navel skin brain, and bone marrow

Symptoms —The symptoms of cancer of the stomach are most indefinite almost any *indigestion* in any individual of cancer age is suspicious Gastric carcinoma is a disease to be kept always in mind and to be excluded only with care and hesitation The *onset* is indefinite the symptoms are slight the disease progresses so stealthily that it is neither suspected nor recognized until it is well advanced The *duration* of symptoms is variable usually it is a few months occasionally it is two or three years rarely it is several years and then of course question arises as to whether the early symptoms should not be attributed to some other cause If so the change in the distress picture may not be recognized by the patient Remissions in the distress are rare the course of the disease being almost invariably progressive

Usually the patient is an individual forty or more years of age who previously has enjoyed excellent health He first notices some *loss of appetite* and consequent *loss of weight* and a very *mild epigastric distress* These symptoms are disregarded for a few weeks or months but they progress and in less than a year he seeks the advice of a physician The weight loss then amounts to 10 or 20 pounds or more The loss of appetite is definite but the patient may not have noticed it The *abdominal distress* consists of fulness or discomfort induced by eating or of gnawing or aching epigastric pain which may appear at any time after eating which not infrequently is relieved by eating and usually is relieved by induced or spontaneous vomiting The pain may follow the identical pattern of peptic ulcer In many cases however the distress of carcinoma is notably different from that of peptic ulcer in that it is present in the morning before breakfast, appears soon after eating and is

not completely relieved by food taking alkali, or even vomiting *Nausea and vomiting* may occur regardless of the location of the lesion, but are much more frequent when the carcinoma obstructs the gastric outlet More or less intractable vomiting of food



Fig 63 —Carcinoma of the antrum Note the characteristic ragged irregular subtraction type of deformity of both curvatures of the antrum The tumor was an ulcerated but *sharply demarcated* (Type II Borrmann) alveolar carcinoma The patient (X—No 7,027) a man forty nine years of age was admitted to the *hospital* January 6 1930 for various symptoms attributed to anemia Loss of appetite and loss *of* weight amounting to 15 pounds had been present for six or eight months An epigastric tumor mass was palpable Moderate anemia occult blood *in the stool* and histamine achlorhydria were present The patient refused operation The loss of weight progressed Vomiting and diarrhea appeared in May and persisted until his readmission to the hospital in September after tarry stools had been present for four days At operation September 13 1930 no metastases were found and a subtotal gastrectomy was performed The patient survived a prolonged postoperative diarrhea and in December a double simple mastoidectomy He remained well until May 1936 when he returned because of malaise and loss of weight The cervical and inguinal lymph glands were enlarged and hard in consistency particularly the so-called Virchow s node above the left clavicle The involved glands were treated with roentgen irradiation but death occurred March 13 1937 over seven years after the diagnosis had first been made and six and a half years after resection of the carcinoma

and gastric juice may be the first symptom of small early intrapyloric tumors The vomitus may or may not contain food blood or bile although the so called coffee ground emesis is particularly suggestive of carcinoma *Hematemesis and melena* may be the first symptom of the disease or occur at any time during its course *Anemia* is often, but not regularly present is almost invariably of the secondary type unless concomitant pernicious anemia exists, and is due to the continual loss of blood from the surface of the tumor *Acute perforation* although uncommon does occur and the surgeon may not suspect the carcinomatous nature of the lesion at the time of the repair An elevation of temperature of 1° or 2° F is not infrequent More marked *fever* does occur and is attributed to a coincident pyogenic gastritis as is evidenced by the histologic demonstration of small abscesses or rarely even by the presence of a phlegmonous gastritis

Examinations —*Physical Examination*—The physical examination is often negative but it may reveal pallor evidence of loss of weight, a palpable movable hard mass in the upper abdomen usually independent of the liver a definite nodular enlargement of the liver a hard enlarged Virchow s node metastatic lesions in the ovaries or on the rectal shelf or rarely in tumors of the fundus of the stomach obliteration of Traube's semilunar space

Laboratory Examination —The laboratory examination may disclose the presence of anemia Free acid is present in the gastric content in about 40 per cent of the cases and after the injection of histamine hydrochloride subcutaneously may be found in rather high concentration 75 to 100 clinical units (*p*H 1 3-1 0) The demonstration of Oppler Boas bacilli and of abnormal amounts of lactic acid in the gastric contents is very strong evidence of gastric neoplasm for these findings occur only when continued retention or stagnation takes place in the stomach with no free acid present that is *with a pH above 3 a combination* of circumstances usually due to carcinoma Occult blood by the benzidine test is present in the gastric content and in the *stool* in 90 to 95 per cent of cases Stool examination therefore gives valuable diagnostic evidence regarding the presence of carcinoma but two possibilities must always be borne in mind first that occult blood if present may not be of gastric origin and second that carcinoma particularly of the infiltrative and scirrhous types may be present in spite of the continued absence of occult blood in the stool Indeed very rarely after massive hem

orrhage the occult blood in the stool may disappear completely for several weeks

X ray Examination —The x ray examination *is probably more valuable in the diagnosis* of gastric carcinoma than any other diagnostic method sign or symptom Although it is not infallible it is constantly improving in accuracy as technic and equipment become better and the proficiency of the roentgenologist increases The classic roentgenologic evidence of carcinoma is the filling defect a rigid constant somewhat ragged alteration in the contour of a portion of the stomach In the antrum both curvatures are likely to be involved and the lumen raggedly narrowed by the infiltration of the wall (see Fig 63) The polypoid tumor growing into the lumen appears as a non opaque nodular mass when pressure is made on the barium filled or partially filled stomach (see Fig 62) Ulceration may be evident from collections of barium caught in the ulcer and typically presenting the appearance of the so-called meniscus sign of Carman (see Fig 64) The normal mucosal pattern is almost invariably distorted or destroyed by the tumor as may be seen from careful mucosal relief studies using small amounts of barium and graduated compression

The roentgenologist not infrequently discovers a dilated stomach with hyperperistalsis yet with obstruction so complete that he is unable to see any barium pass through the pyloric channel and hence is unable to ascertain the exact location or nature of the lesion The problem in such a case is usually the differentiation of a pyloric carcinoma from a duodenal ulcer with high grade stenosis The obstruction is rather more likely to be complete with carcinoma than with ulcer and of course the duration of symptoms as well as the other diagnostic criteria are very helpful

In all cases *the roentgenologic evidence* must be carefully weighed and evaluated by itself and in conjunction with the clinical data

Gastroscopic Examination —Gastroscopy is of value in confirming the roentgenologic diagnosis of carcinoma or not infrequently in providing definite evidence bearing on a questionable roentgenologic finding Occasionally a tumor may be demonstrated with one method and not with the other Gastroscopy may give important information with regard to the type of the tumor its *operability and the prognosis* Gastroscopically, tumors are seen in picturesque forms and in colorings much more brilliant than those seen at autopsy or in the resected specimen The polypoid tumors are usually seen easily and are readily recognized although occasionally it is difficult to differentiate them from benign tumors or hypertrophic gastritis If ulceration is present however



Fig 64 —Ulcerating carcinoma of the lesser curvature The crater lying beneath the line of the lesser curvature is surrounded by the ragged nodular halo produced by the polypoid infiltrated wall The roentgenologic diagnosis was an ulcerating Type II gastric neoplasm the gastroscopic diagnosis was huge ulcerating Type III carcinoma of the posterior wall and lesser curvature Subtotal gastrectomy was carried out The tumor was a well localized ulcerating polypoid carcinoma measuring about 5 × 7 cm The patient, X—No 67633 a female forty four years of age had had left upper quadrant distress for six months and had lost 34 pounds in weight. The blood count was normal Histamine achlorhydria was present

the carcinomatous nature of the lesion is apparent for the irregular ulcer floor covered with pieces of necrotic tissue dirty *gray greenish gray brown red or violet in* color is surrounded by a thick wall usually dark red in color and sharply demarcated from the normal gastric tissue When the margin of the ulcer is seen to fade gradually into infiltrated tissue which in turn blends imperceptibly with the normal gastric mucosa the lesion is usually an infiltrating ulcerating tumor of Type III or IV Certain infiltrating carcinomas may be im

possible to differentiate gastroscopically from lymphosarcoma, lymphogranuloma, leukemia, syphilis or hypertrophic gastritis

Diagnosis—The importance of carefully examining all patients in middle life and beyond who have continued abdominal distress cannot be overemphasized The symptoms of carcinoma while usually suggestive, are *not diagnostic The physical and laboratory* examinations may yield corroborative, although as a rule not pathognomonic evidence The roentgenologic and gastroscopic examinations give more exact and precise information The diagnostic accuracy of the complete clinical study is very great—so great indeed that "exploratory laparotomy as a diagnostic procedure in gastric disease is rarely indicated In fact the evidence gained by palpation and inspection of the

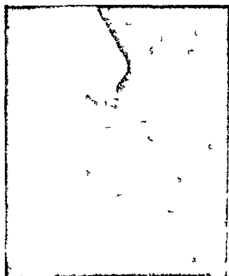


Fig 65 — Leather bottle stomach Note the small uniformly contracted stomach giving the appearance of a stomach in miniature the dilated esophagus and the rather well filled duodenum The patient (X—No 156548) a male fifty five years of age had had stomach trouble off and on for several years with swelling of the abdomen beginning two months prior to admission for which paracentesis was required Death occurred two months after the above roentgenogram was taken

stomach at operation may be less reliable than that obtained preoperatively

Course—The course of gastric carcinoma is invariably progressive the symptoms are likewise progressive although they may exhibit in rare instances remarkable fluctuations and remissions The *clinical course* of the disease usually covers a period of from twelve to thirty months but it may be only a few weeks, almost acute' or it may last several years, being in a sense 'chronic Death comes usually from inanition with prolonged anorexia vomiting and weakness

Prognosis—The prognosis depends upon the type and location of the tumor and upon the resistance of the individual It is important to know that in general the polypoid *sharply circumscribed neoplasms* growing into the lumen (Type I of Borrmann Moskowicz Konjetzny, Schindler) (see Figs 6? 63, 64) are much slower in their growth than are the infiltrative ones (Types III and IV) (see Fig 65) although exceptions do occur Some papillomatous carcinomas metastasize early, and conversely the infiltrating carcinoma fibrosum, producing the so-called linitis plastica may run a very slow course metastasizing late or not at all The diffusely infiltrating carcinomas of Jarcho on the other hand produce very small local lesions and metastasize early the metastatic tumors in the bone marrow or elsewhere giving rise to symptoms before the primary growth does so

The histologic grading of *malignancy* (Broders) may be helpful in that on the whole the degree of differentiation and the grade of malignancy are inversely proportional to each other Different sections from the same tumor however may disclose varying degrees of differentiation And indeed a highly differentiated colloid carcinoma may rarely be very malignant

The location of the neoplasm is of prognostic importance in several respects Carcinomas of the pylorus (intrapyloric tumors) produce obstruction and symptoms earlier than do those in the body of the stomach and are easily resected Tumors of the distal third of the stomach may be resected more easily than those of the middle *third* and these in turn are much more easily resected than those of the upper third or cardia Carcinomas of the greater curvature tend to be more easily resectable than those of the lesser curvature because the involvement of the deeper lymph glands occurs at a later stage in the disease and also because the primary growth is as a rule most accessible

The *resistance* of the individual to carcinoma is unpredictable but there is evi

dence that the body does exhibit a certain ability to resist or even destroy cancer cells Years after the resection of a gastric carcinoma cellular nests of carcinoma may be found locked in the scar tissue no other metastases being demonstrable

The prognosis is not influenced by sex and on the whole not greatly by age although in general carcinoma is said to progress more rapidly in the young more slowly in the aged However the longest cure in the Breslau clinic (twenty one years) was observed in a young man thirty one years of age The duration of life after resection of a gastric carcinoma averages one to two years longer than in cases treated with palliative medical measures only or indeed with other forms of surgery So called three year cures after resection are frequent five year cures are not infrequent and cures of longer duration do occur as in the case mentioned above

Treatment —There is at the present time only one real treatment for gastric carcinoma and that is surgical removal

Surgical Removal —CONTRAINDICATIONS TO OPERATION —There are available preoperatively very few criteria sufficiently positive to justify a decision against exploratory laparotomy— exploratory in the sense that the operation is undertaken to determine what can be done surgically Advanced age is not a contraindication for the operation is one not of choice but of necessity Weakness cachexia heart disease and other associated conditions likewise do not constitute contraindications Preliminary blood transfusions and parenteral clyses of normal saline in amounts of 2000 to 3000 cc daily usually bring sufficient improvement in the general condition of the patient to warrant operation within a few days Definite contraindications are limited to the presence of proved metastatic lesions such as a carcinomatous peritonitis neoplastic infiltration of the liver or metastases to the bone marrow Great caution is necessary for a nodular liver may be a cirrhotic liver independent of the gastric tumor

RESECTABILITY —The circumscribed polypoid Type I carcinomas are usually resectable whereas the infiltrative Types III and IV are more likely to extend along the esophagus or to involve adjacent structures such as the liver or pancreas The surgeon may be able to find a line of cleavage and remove the tumor but recurrent growths almost invariably develop The prognosis after resection is much better in Types I and II than in III and IV, except for certain rare exceptions such as the highly malignant papillomatous tumors on the one hand and the very slow growing carcinoma fibrosum on the other However regardless of the gross or histologic appearance all gastric carcinomas should if possible be resected even a complete gastrectomy being at times justifiable The presence of large lymph glands is not a contraindication to resection because the enlargement may be inflammatory rather than neoplastic and because life is usually prolonged by resection even if lymphatic spread has taken place Metastases in the liver or distant lymph nodes likewise do not necessarily constitute a contraindication to resection for the operation may prolong life even under these circumstances and may lead eventually to a less agonizing death than that resulting from pyloric obstruction In rare instances the patient may be definitely benefited by the removal of a gastric carcinoma and simultaneous extirpation of metastatic lesions elsewhere such as ovarian (Krukenberg) implantations

MORTALITY RATE —Existing statistics on operability and on surgical operative mortality are of little value because they are based upon three variables—the patient the surgeon and the tumor The mortality rate rises as the removal of the more extensive tumors in the more debilitated patients is attempted The best surgical risk is the individual with a small intrapyloric growth producing acute obstruction early If resection is undertaken only in cases of this type the mortality rate should be very low whereas if the surgeon undertakes to remove all carcinomas even though a complete gastrectomy is required, the hazard of the operation is necessarily greatly increased In some institutions a mortality rate of 10 per cent is arbitrarily considered satisfactory a lower rate indicating that too few resections are being undertaken and a higher rate too many Obviously the skill and experience of the surgeon influence both the percentage of cases in which resection is

attempted and the mortality rate It is important to emphasize the fact that the mortality rate alone is not a satisfactory index of immediate surgical results for it must always be evaluated in terms of the per cent of total cases submitted to operation and the per cent in which resection is attempted Exploratory laparotomy *per se* has a definite hazard and very little therapeutic value gastro enterostomy has a certain palliative effect, *resection* alone offers the patient the chance of a cure Consequently a high mortality rate with a high incidence of resection may be preferable to a low mortality rate with a low incidence of resection

Palliative Treatment—Various palliative procedures may be employed in inoperable tumors and in patients refusing surgical aid

GASTRO ENTEROSTOMY in inoperable obstructive tumors may give the patient an interval of six to eighteen months of fairly good health with symptomatic relief and a gain in weight before the inevitable decline again becomes manifest

RADIATION THERAPY has produced some striking morphologic changes in certain gastric carcinomas and has been found very valuable in the treatment of lymphoblastoma and other malignant mesenchymal gastric tumors but no satisfactory proof exists that it has ever cured a single case of gastric carcinoma The nausea, vomiting and weakness resulting from the therapy usually accelerate the downward course of the patient Radiation can therefore not be recommended either as a therapeutic or palliative procedure On the other hand the destructive effect of the roentgen ray on neoplastic cells cannot be denied and hence in time a means may be found for utilizing it in the prevention or treatment of gastric carcinoma The value of postoperative radiation after resection remains to be fully assessed but it seems to prolong the survival period

SYMPTOMATIC TREATMENT varies from day to day and from patient to patient Rules cannot be laid down The needs of the day must be met as they arise with the various diets drugs and procedures available but above all with kindness and sympathy and with as much encouragement and cheerfulness as possible The physician must endeavor to support the waning courage of the patient and thus help him carry on as bravely as possible

The *diet* should be palatable and nutritious Restrictions should not be imposed. In some cases particularly those with acid gastric juice the *antacid ulcer management program of Sippy* may afford partial or complete symptomatic relief for several weeks or months Suggestion and other forms of psychotherapy are occasionally strikingly effective for a short time Sedatives analgesics hypnotics and narcotics should be used unhesitatingly but judiciously The parenteral administration of fluid and rarely blood transfusions may be indicated

The Patient, the Physician, and the Truth—The difficult question as to whether or not the patient should be told the true nature of his disease cannot be answered categorically Patients and physicians have various opinions in this regard The patient with carcinoma is not likely to accept the truth if told it as philosophically as he himself had planned Certainly the patient should be told enough to ensure the proper treatment Usually it is sufficient to state simply that an operation is necessary for obstruction or for tumor A responsible member of the family should always be informed frankly and fully not only of the presence and nature of the disease but also of the prognosis and the therapeutic possibilities The word cancer should not be used to the patient and usually not to the relatives if it can be avoided for to most people it has only the most terrible connotations The fear of cancer is so great that many patients if told they have cancer immediately abandon all hope and in utter panic refuse to make any attempt to deal with it intelligently The public is not yet sufficiently aware that cancer may be curable The patient told that he has a 'growth may well understand that he has a cancer but he prefers not to press the point The responsible relative is more likely to do so and of course should be told If however the patient refuses operation and particularly if he does so when the physician considers that the tumor is *likely* to prove resectable the facts should be presented fully and frankly The patient may still refuse surgical treatment and it *is* his privilege to do so but usually he accepts

the advice given If he survives resection it is better not to inform him of the likelihood of recurrence If the tumor cannot be resected it is not necessary to tell the patient that he is doomed A certain vagueness leaves a ray of hope whereas complete frankness may be terribly brutal Honesty as a moral law does not justify brutality and honesty after all is purely relative The physician must remember also that mistakes are made that his diagnosis may be wrong and that strange things are seen in the practice of medicine Usually the situation can be handled in such a manner as to avoid frank discussion of the nature of the disease its course and prognosis The patient may fear the worst but usually he finds courage to hope that the condition is not as bad as he fears The physician with kindness sympathy, courage and resourcefulness must travel the road with the patient relieving his distress as much as possible and supporting his morale until finally the journey ends before the patient realizes that death is at hand

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PEPTIC ULCER

(Digestive Corroding Eroding Simple Round Perforating or Acid Ulcer)

Definition —Peptic ulcer is a sharply circumscribed loss of tissue beginning in the mucosa extending through the submucosa into the muscular layers of the esophagus stomach or intestine and resulting from the failure of the mucosa to withstand the digestive action of acid gastric juice The first clear description is usually attributed to Cruveilhier (1829) whose name it bore for many years as the round ulcer of Cruveilhier" but Matthew Baillie pictured the lesion in a series of engravings published in 1799 and John Abercrombie wrote an excellent account of the symptoms in 1828

Distribution —The geographic distribution of peptic ulcer is world wide the lesion occurs in all races of men The incidence of the lesion is reported to vary in different countries but the statistics are open to question It occurs among all occupations, workers and nonworkers

Incidence —The exact incidence of peptic ulcer in man is unknown although it is estimated on the basis of autopsy statistics that approximately 10 per cent of all individuals suffer at some time in their lives from a chronic gastric or duodenal ulcer At autopsy the gastric lesion is more frequent than the duodenal but duodenal ulcer is much more commonly encountered clinically For some unknown reason, males are afflicted about four times more frequently than females

The lesion occurs at all *ages* Acute ulcers producing melena neonatorum and acute perforation are not uncommon in the newborn Unless these complications are present chronic ulcer is rarely diagnosed during the first decade of life although its incidence is probably greater than is generally appreciated Between the ages of twenty and fifty peptic ulcer is very common after fifty it is also frequent Striking instances of an *hereditary* or *familial tendency* are encountered but perhaps not more often than might be expected on the basis of coincidence The typical ulcer patient is usually described as a lean individual of a definite *constitutional type* contrasting with the short stocky obese so called gallbladder type As a matter of fact peptic ulcer and cholelithiasis are seen in all constitutional types and not infrequently in the same individual

Morbid Anatomy —*Location* —Peptic ulcer occurs in the lower part of the esophagus in the stomach in the upper portion of the duodenum in the small bowel adjacent usually to a patent gastro enterostomy or a Meckel s diverticulum and very very rarely elsewhere in the jejunum or ileum The lesion occurs in constant association with normal or ectopic gastric mucosa The vast majority of peptic ulcers occur along the

lesser curvature of the stomach, the so called 'magenstrasse,' or in the first 3 or 4 cm of duodenum the duodenal bulb The pylorus is not infrequently involved, prepyloric and postpyloric lesions are rather common The greater curvature of the stomach is a very rare site for benign ulcer

Pathologic Description—Ulcers are usually single but not infrequently they are multiple being present in both the stomach and duodenum or as multiple lesions in either organ such as the so called kissing ulcers of the anterior and posterior walls of the duodenum Active and healed lesions may coexist The average diameter of the gastric ulcer is 5 to 25 mm, although the lesions may be only 2 or 3 mm in diameter or as large as 40 to 60 mm In the duodenum and jejunum the diameter usually varies from 2 to 10 mm, rather rarely reaches 15 mm and quite rarely 20 or 30 mm The depth is variable often 10 to 20 mm in the stomach, usually 2 to 6 mm in the duodenum The lesion differs from an erosion in that it involves not only the mucosa but also the muscularis mucosae Peptic ulcer is the result of a penetrating process beginning in the mucosa invading the deeper layers of the gastric wall and perhaps, perforating them completely It may be acute or chronic the essential difference pathologically being the amount of connective tissue present The border of the ulcer is sharp the surrounding mucosa may be normal or slightly inflamed flat or slightly elevated or even rounded due usually to extensive edema of the submucosa or rarely to fibrous tissue The floor of the ulcer is clean and consists of a thin layer of fibrinopurulent exudate overlying a narrow zone of fibrinoid necrosis and a deeper zone of granulation and fibrous tissue In chronic ulcer the muscular layer in the base is usually interrupted completely by fibrous tissue and the blood vessels are thrombosed The capsule of the liver or pancreas may form the base of the ulcer, or indeed the lesion may invade these organs Evidence of extension and healing may be found together although usually ulceration or repair is dominant at a given time the one leading to further ulceration perforation or hemorrhage and the other to quiescence and healing with scar tissue proliferation growth of a thin layer of mucosal cells across the defect and the eventual transformation into a normal mucosa The life history of an ulcer with its characteristic periods of remission and exacerbation is thus evidenced pathologically by phases of more or less extensive ulceration and more or less complete healing

Carcinomatous Degeneration of Benign Ulcer—The subject of carcinomatous degeneration in peptic ulcer has been a very controversial one as regards both its occurrence and its alleged incidence The question arises in connection with gastric ulcer only Primary carcinoma of the first portion of the duodenum is very rare although carcinoma elsewhere in the duodenum is not so rare Carcinoma of the jejunum adjacent to a gastro enterostomy stoma is also so rare that the question of malignant degeneration of a jejunal peptic ulcer has scarcely arisen Although various explanations have been given for the alleged tendency of gastric ulcers to undergo malignant transformation in contrast with duodenal ulcer the evidence available suggests that benign peptic ulcer does not undergo malignant degeneration at all, but that gastric carcinoma on the other hand does at times undergo peptic digestion and may mimic the benign lesion in almost every respect This explanation is in accord with the high incidence of gastric cancer the almost complete absence of primary carcinoma of the bulb and the rarity of carcinoma of the duodenum and jejunum There is clear evidence that peptic digestion may almost completely destroy a gastric carcinoma and produce a lesion grossly identical with benign ulcer It must be admitted on the other hand that the possibility of carcinomatous degeneration of a benign ulcer cannot be denied even though proof of its occurrence is lacking From the practical point of view however the consideration is of very little significance in comparison with the question as to whether a given lesion is benign or malignant The important problem is the differentiation of the two lesions

Curling s Ulcer—Curling s ulcer is a special lesion an acute gastroduodenal ulceration following extensive burns of the skin The phenomenon was described by Swan in 1823 and later by Lang but Curling called attention to it

sexes at all ages, usually near the pylorus may be single or multiple usually causes pain nausea and vomiting within a few days after the burn and may be complicated by acute perforation or hemorrhage The lesion is as a rule not diagnosed clinically but is found at autopsy In rare instances a chronic ulcer may result The mechanism of production is unknown It may be related to an increased gastric secretion as a result of a systemic histamine reaction secondary to the burn

Association with Other Diseases—Peptic ulcer occurs in conjunction with practically all diseases the notable exceptions being those characterized by a complete achlorhydria particularly pernicious anemia and combined column degeneration of the spinal cord In the milder grades of atrophic gastritis acid gastric secretion and peptic ulcer may be found but in the more severe forms achlorhydria usually obtains and peptic ulcer is not present Superficial and especially hypertrophic gastritis are commonly found in patients with ulcer Gastric carcinoma or neoplasm of any type located anywhere in the body may be observed coincident with active or healed ulcer Special reference should be made perhaps to the lesions occurring in patients with tumor of the brain particularly after operation although their exact frequency and significance are open to question Primary secondary tertiary and latent syphilis including tabes dorsalis and general paresis are seen in approximately their anticipated frequency in patients with ulcer Polycythemia thrombo angiitis obliterans heart disease of all kinds essential hypertension pulmonary tuberculosis as well as all acute and chronic infectious diseases hyperthyroidism and diabetes mellitus—all occur in patients with peptic ulcer or vice versa In pregnancy ulcer rarely develops and the symptoms of ulcer if present previously usually subside In diaphragmatic hernia erosions or ulcers are likely to develop at the constricting ring Occasionally ulcer is seen in patients with hepatic cirrhosis the incidence is not significant nor is that of ulcer with cholelithiasis Duodenal stasis as evidenced by a rather wide descending or second portion of the duodenum with so called puddling and reverse peristalsis is a phenomenon seen frequently in normal individuals in fact it is almost invariably present in patients with long thin abdomens and a narrow costal angle and hence is frequently observed in patients with peptic ulcer Renal calculi appear to be somewhat more frequent in patients receiving alkali therapy for peptic ulcer than they are in normal persons although this point is not definitely established Acute appendicitis is a common complication of antacid ulcer management due presumably to the formation of enteroliths in the appendix followed by obstruction and resultant increase in the intraluminal pressure as shown experimentally by Wangensteen

Etiology and Pathogenesis—Peptic ulcer has been ascribed to various causes including bacterial and nonbacterial inflammation trauma infarction chemical action and neurogenic mechanisms

Bacterial Inflammation—Acute ulcers are found not infrequently at autopsy in patients dying from acute infectious disease but thus far all attempts to isolate a specific micro organism have been unsuccessful Various bacteria have been isolated from the floor and acute lesions have been produced by the injection of different organisms but typical chronic ulcer results only occasionally not with convincing regularity

Nonbacterial Inflammation—The concept of nonbacterial inflammation as the cause of ulcer is supported chiefly by the histologic evidence of chronic nonspecific gastritis so called antral gastritis in all cases of peptic ulcer Indeed cases have been described pathologically as ulcer disease without ulcer with symptoms indistinguishable from those seen in patients with ulcer There are certain objections to this theory one of the major ones being that gastroscopic evidence of gastritis is frequently lacking in patients with peptic ulcer Furthermore if gastritis were shown to be the forerunner of ulcer the cause of the gastritis would remain to be explained

Trauma—Direct epigastric trauma is occasionally followed by the prompt appearance of the symptoms of ulcer and indeed by its subsequent roentgenologic demonstration but there is no other evidence that it plays any role in the pathogenesis in the vast majority of cases

Infarction—The concept of vascular occlusion as the cause of ulcer is based on the craterlike appearance of the lesion and the demonstration of thrombosed vessels in the base Unsatisfactory hypotheses such as vascular spasm are advanced to explain the thrombosis, although this is apparently the result rather than the cause of the lesion It is not possible to produce chronic ulcers by ligation of the gastric vessels, for approximately 90 per cent of the blood supply to the stomach may be interrupted without producing necrosis of the mucosa

Peptic Digestion—The chemical theory of ulcer formation is based on the recognized ability of the gastric juice to digest living tissue as shown by Claude Bernard s classic experiment with the frog s leg Many theories have been offered to explain the normal ability of the gastric mucosa to resist digestion but apparently the thin layer of mucus constantly secreted by the mucus secreting cells affords the chief protection The evidence that chronic peptic ulcer is in some way related to acid gastric juice seems conclusive Clinically, chronic ulcer is found only in those portions of the digestive tract exposed to the action of acid gastric juice Furthermore it is found only in individuals whose gastric glands are able to secrete acid It is a highly significant fact that the 10 per cent of the population with histamine achlorhydria do not develop ulcer Experimentally ulcer may be produced by various operations interfering with the normal neutralization of the acid by the duodenal content by the administration of acid or by the continuous stimulation of acid gastric secretion by means of the intramuscular injection of a mixture of histamine and beeswax The pathologic clinical and experimental evidence are in accord in indicating that peptic ulcer is a penetrative process beginning in the mucosa and dependent upon the destructive action of acid gastric juice The explanation of the failure of the mucosa to withstand the acid attack is not clear

Neurogenic Theory—The neurogenic theory of ulcer formation has been advanced because ulcers are so frequently seen in nervous individuals or in relationship to emotional disturbances because the lesion is occasionally observed as a postoperative complication in patients with brain tumors and because acute erosions and ulcerations in the stomach follow the experimental production of certain intracranial lesions The explanation of these observations is not clear

Summary—Peptic ulcer is the product of pathologic physiology, it results from the failure of the mucosa to resist the destructive action of acid gastric juice The factors responsible probably include lack of cellular resistance a lack of cellular protection, as might result from an insufficient secretion of mucus or excessive acid gastric juice particularly during the night and during the fasting periods when the normal stomach secretes very little acid The central nervous system through the vagus may play a very important role by the production of hypermotility and quantitative hypersecretion These basic problems remain to be elucidated

Symptoms—*Pain* is the outstanding symptom of ulcer A thorough understanding of the distress of peptic ulcer is in the words of Sippy, the key to the analysis of abdominal pain The four characteristic features of the pain of peptic ulcer are its *chronicity* its *periodicity* its *quality* and its *relationship to food taking*

The CHRONICITY of the disease is indicated by the fact that the average stated duration of the distress is six or seven years in occasional cases the symptoms are of only a few days or weeks duration in others they may have existed for forty or fifty years

The PERIODICITY of ulcer distress is striking The usual statement is that the attacks come in the spring and the fall As a matter of fact the greatest incidence occurs in the months from October to March inclusive with an additional peak in June The significant point is not the season of the year but the periodicity of the distress The symptoms may last for a few days several weeks or several months and the periods of remission be of similar duration As time goes on the tendency is for the periods of distress to become more frequent and of longer duration whereas the remissions are less frequent and shorter *Precipitating* causes of the exacerbations are usually listed as acute infections, worry and fatigue although Moynihan included exposure to cold getting

the feet wet or the eating of a hasty and indigestible meal These unavoidable accidents of living are so common and so universal that one doubts their causal relationship to the formation or reactivation of an ulcer

The QUALITY of ulcer distress although rather variable tends to conform to a definite pattern It is as a rule a gnawing or aching sensation sometimes it is described as burning hurting annoying or cramplike or indeed as hunger It differs from the intermittent pang of true hunger in that ulcer distress is almost invariably steady and continuous for periods of fifteen minutes to an hour or more unless measures are taken to give relief Moynihan referred to ulcer pain as a hunger pain purely because of its relationship to food taking In severity the pain varies from a very mild discomfort to acute pain It is almost invariably epigastric usually sharply localized to an area a few centimeters in diameter to which the patient points with the tips of the fingers The pain may radiate around the costal border or through to the back or to the right lower quadrant or very rarely to the navel or below In duodenal ulcer the distress is likely to be located in the right epigastrium in gastric ulcer in the left epigastrium and in jejunal ulcer in the left mid abdomen or even in the left lower quadrant The presence of pain in the back suggests but does not prove the presence of chronic perforation

The *rhythm of pain* in peptic ulcer is related to the digestive cycle and is the same for both gastric and duodenal ulcer A detailed analysis of a typical day provides valuable information and should be incorporated in the history Pain attributable to ulcer is almost invariably absent in the morning before breakfast appears one to four hours after breakfast and lasts thirty minutes or more perhaps until relief is obtained at the noon meal The distress recurs one to four hours later and is then usually more severe than in the forenoon The afternoon pain may likewise disappear spontaneously but more frequently definite measures are employed to bring relief the patient having learned that the taking of food or alkali in adequate amounts vomiting or rest usually affords relief In the evening the pain may recur one to four hours after eating but it is often less severe than in the afternoon The same measures give relief The patient may be awakened with pain usually between 12 and 2 A M Rarely does nocturnal pain appear unless pain has been present in the evening and rarely indeed does pain attributable to ulcer develop later in the night unless it has been present earlier and relieved by food or alkali The presence of nocturnal pain is often interpreted as evidence of pyloric obstruction or high grade stenosis but it is also seen in nonobstructive acutely inflamed lesions with highly acid gastric secretion

Mechanism of Pain in Peptic Ulcer—The normal gastric mucosa is insensitive to cutting pinching tearing or exposure to varying hydrogen ion concentrations The inflamed mucosa on the other hand may be sensitive due apparently to a lowering of the pain threshold The pain of peptic ulcer depends primarily therefore, upon the degree of inflammation present in or about the lesion An acutely inflamed ulcer is highly sensitive to mechanical or chemical trauma in the form of peristalsis and spasm or changes in the hydrogen ion concentration The role of acid gastric juice in the pathogenesis of peptic ulcer has already been presented but it is important to point out that the acid juice evokes a chemical inflammation in the mucosal defect lowers the pain threshold of the nerve endings and produces pain When the defect is protected from the action of the acid the inflammation subsides the sensitivity decreases and the pain disappears The pain seems to arise directly at the site of the lesion not in some distant part of the stomach or duodenum or through any vague reflex mechanism The importance of the acid factor in the mechanism of pain in peptic ulcer is shown by the following observations

1 When pain attributable to ulcer is present a high degree of free hydrochloric acid is practically always found in the stomach

2 The pain is relieved by any measure which neutralizes the acid

3 The pain may be relieved by emptying the stomach and in sufficiently sensitive lesions be caused to reappear by reinjection of the acid chyme whereas the injection of the gastric content in which the free acid

ity has been neutralized does not produce pain

4 Ulcer pain typical in kind location and severity, may be produced under suitable conditions by the injection into the stomach of dilute solutions of hydrochloric acid in perfectly physiologic concentrations (0 2–0.3 per cent)

5 Ulcer pain under proper conditions may be induced by the injection of acid gastric juice from another patient or by stimulation of the patient's own gastric secretion by histamine

The concentration of acid at the time of the pain is not abnormal nor is it greater than that present in the same stomach without pain when the ulcer is healed or in a healing phase The presence of pain at any given moment therefore, is dependent upon the presence of an inflamed lesion and acid gastric juice Theoretically the former could occur without the latter practically it does not and probably for the reason that the inflammation of peptic ulcer results from the continued action of acid gastric juice The question is often raised as to why ulcers may be present may bleed profusely and may perforate without antecedent pain The only apparent answer is the rather vague and unsatisfactory one of a high pain threshold and low sensitivity

Atypical Distress—The classic ulcer history as outlined is frequently not obtained The usual reason is that the patient is a poor observer or insufficient care has been taken in describing the symptoms When a careful diary is kept or when the patient is hospitalized and the sequence of pain studied, it almost invariably conforms to the description given Exceptions occur in acutely inflamed lesions presumably with more or less *perigastritis* and *periduodenitis* In such cases the pain may be only partially relieved by food taking or by alkali or by the emptying of the stomach the incompleteness of the relief being due to a persistent soreness and tenderness which disappears in a few hours or days if neutralization of the acid is maintained

The so called *biliary* or *tabetic* types of ulcer distress in which there is a severe steady continuous pain accompanied by vomiting and simulating both biliary colic and the gastric crisis of tabes dorsalis constitute an important variant of the usual picture The attack may last for several days with continued pain nausea, and vomiting The vomitus consists of clear or bile-colored *highly acid* gastric juice in marked contrast with the viscid emesis of continued biliary or tabetic vomiting Slight jaundice is occasionally seen with peptic ulcer, presumably due to cholangitis

Accessory Symptoms—NAUSEA is not a common symptom of ulcer, although it may occur and not be accompanied by pain

EMESIS may result from severe pain, although usually the vomiting is caused by obstruction—spastic inflammatory, or cicatricial Painless vomiting may occur in high grade obstruction or more rarely in nonobstructive lesions in which case it is presumably due to a reflex disturbance of the intrinsic neuromuscular coordination

WATER BRASH is a rather rare symptom consisting of a combination of excessive salivation and acid regurgitation sometimes awakening the patient at night

The APPETITE and WEIGHT are usually well preserved but marked loss of weight, amounting to 30 to 40 pounds may result from continued vomiting or the patient's fear of eating On the other hand the frequent ingestion of food in order to relieve the pain may result in a gain in weight

CONSTIPATION is a common complaint usually associated with a cathartic habit the symptoms of which may completely obscure the distress of ulcer

DIARRHEA is rare except in the presence of a gastrojejunocolic fistula which may develop gradually or suddenly after gastroenterostomy and without any pain whatsoever The SIGNS AND SYMPTOMS OF ANEMIA may or may not be present in peptic ulcer if present they may develop gradually or acutely Occasionally chlorosis is erroneously diagnosed in such cases

Examinations —*Physical Examination*—In peptic ulcer the anamnesis is everything the physical examination nothing (Moynihan) although of course even negative findings are important Localized tenderness is not uncommon occasionally the outline of a distended stomach may be made out and peristaltic waves observed very rarely a tender mass may be palpable

Laboratory Examination—As in the

physical examination normal conditions are to be anticipated unless some complication is present The demonstration of acid gastric juice is essential because chronic peptic ulcer does not occur in its continued absence Sarcinae or yeastlike organisms in the gastric content are indicative of long con

Mistakes are made however both of omission and commission The roentgenologic evidence must be weighed and its value assessed by the clinician in conjunction with the other data available

The roentgenologic signs of ulcer are usually divided into the direct or primary signs

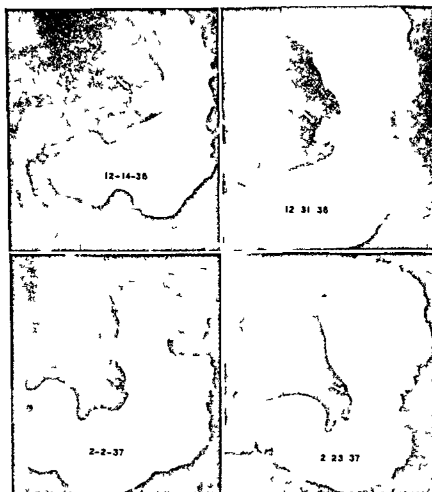


Fig 66—Spectacular healing of gastric ulcer The enormous crater present December 14 1936 was barely visible February 23 1937 Gastroscopically the lesion appeared to be almost healed at this time but complete disappearance was not reported until April 7 1937 The patient Unit No 165135 a female sixty three years of age gave a history of epigastric pain radiating through to the back between the shoulder blades unrelated to food relieved only by emesis and accompanied by more or less persistent vomiting for sixteen days Periodic postprandial epigastric distress had been present for eleven months and several similar attacks had occurred in the preceding thirty five years

tinued obstruction Occult blood may be found in the gastric analysis or in the stool but it is more often absent than present

X ray *Examination*—In peptic ulcer the x ray is the most important diagnostic procedure In proper hands and under suitable conditions probably 95 per cent of all ulcers may be demonstrated roentgenologically

and the indirect or secondary The *primary signs* are relatively pathognomonic and consist of the demonstration of the crater of the ulcer or the deformity produced by it or both whereas the *secondary signs* consisting of such nonspecific findings as gastric retention altered peristalsis and localized tenderness are relatively unimportant In

the stomach the crater is usually seen as a penetrating niche in profile (Fig 66), whereas in the bulb it is more frequently seen *en face* (Figs 67 69) The crater is the only definite roentgenologic evidence of active ulcer It can be demonstrated in at least 90 per cent of the cases of active gastric ulcer in from 50 to 70 per cent of those with active duodenal ulcer and probably in the majority of cases of anastomotic ulcer True craters may occur at any point along the lesser curvature of the stomach in the ture is seen, whereas in the duodenum the process typically causes some contraction and hence a deformity of one or both curvatures of the bulb (Figs 68 69)

Gastroscopic Examination —This method enables one to inspect the gastric mucosa and often permits the demonstration of small lesions not visible roentgenologically Its great disadvantage lies in its inability to see beyond the pylorus

Diagnosis —The diagnosis of peptic ulcer is based upon the clinical syndrome de-

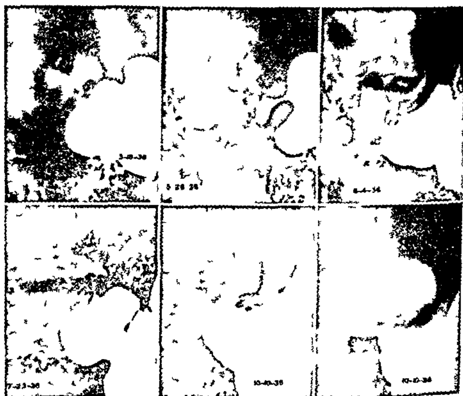


Fig 67 —Active duodenal ulcer showing an *en face* view of a large crater in an undeformed bulb Under treatment the crater decreased rapidly in size from May until October and in healing left no residual evidence of deformity The patient, X—No 48157 a male university student, nineteen years of age had experienced dull aching epigastric pain coming on three or four hours after eating for only three weeks before his admission to the hospital

bulb or even in the proximal part of the second portion of the duodenum In profile the crater appears as a penetrating niche *en face* it is a sharply outlined and circumscribed collection of barium usually 2 to 10 mm in diameter and surrounded by a clear halo The rugae or gastric and duodenal folds typically radiate to it As the ulcer heals its site may be indicated by the radiating folds In the stomach healing rarely alters the contour of the organ except in those cases in which an hour glass contrac

scribed and upon the direct roentgenologic or gastroscopic demonstration of the lesion The greater the skill of the roentgenologist the less the frequency with which a positive diagnosis will be justified without confirmatory roentgenologic evidence The differential diagnosis of a demonstrable gastric or duodenal lesion is usually not difficult for the criteria described are on the whole quite characteristic The most difficult task actually encountered is the differentiation of benign and malignant gastric ulcer

Differentiation of Benign and Malignant Gastric Ulcer—The criteria available for the differentiation of these two lesions are of relative not absolute value There are certain signs as pointed out previously more or less diagnostic of gastric cancer whereas there are none pathognomonic of a benign process unless it be the proved healing of the lesion Age is of some importance although carcinoma may occur in the third decade and benign ulcer is not uncommon in the sixth and seventh A long history of several years duration suggests a benign lesion and a short one malignancy but carcinoma may arise in a patient with chronic indigestion of whatever cause and conversely benign ulcer often develops acutely and gives a short history A qualitative or quantitative change in a chronic distress is sometimes considered as evidence of malignancy but this occurs in a benign lesion also Periodicity is usual in ulcer rare in carcinoma The relationship of the distress to food taking alkali or emesis so classically typical of peptic ulcer is likewise frequently seen in carcinoma Loss of appetite is much more likely to occur in cancer although marked loss of weight and strength may occur in both conditions Hematemesis coffee ground vomitus and melena may be the initial symptoms in either The continued presence of occult blood in the stool after two or three

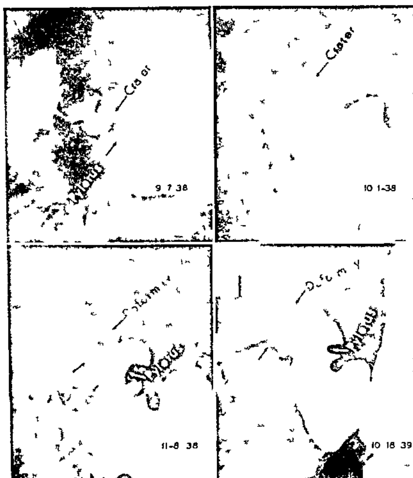


Fig 68—Healing duodenal ulcer Note the marked decrease in the size of the crater as seen in the compression views between September 7 and October 1 The residual deformity is well seen in the film of November 8 The apparent increase in the width of the channel between November 8 1938 and October 18 1939 is more apparent than real for the film obtained November 8 shows the bulb in a phase of contraction whereas that of October 18 shows a filled, although deformed bulb The patient X—No 68292 a male twenty three years of age had had epigastric distress for five years and several massive hemorrhages Histamine free acidity 115

weeks of careful treatment is presumptive evidence of malignancy whereas the continued absence of occult blood suggests that the lesion is benign although exceptions of both kinds occur The demonstration of histamine achlorhydria speaks almost unequivocally against a benign ulcer as does the presence of large numbers of Oppler Boas bacilli and lactic acid High acid values such as 100 or 110 after histamine (pH 1 0) are not infrequently seen in carcinoma

The *x-ray interpretation* of the nature of a gastric ulcer is valuable it depends upon certain considerations such as location size and depth relationship to adjacent structures and the character of the surrounding mucosal pattern Ulcers of the greater curvature are almost always malignant Indeed the greater the distance of the lesion from the lesser curvature the greater is the probability of its being malignant but on the other hand many ulcers of the lesser curvature are also malignant Size is of relatively little value, for small lesions may be carcinomatous and large craters are often benign The meniscus sign of Carman consisting of an ulcer crater located beneath the level of the lesser curvature and demarcated by a zone of tumefaction appearing as a halo almost invariably denotes carcinoma for benign craters usually extend beyond the lesser curvature (Compare Figs 64 and 66) The halo however may be seen in both lesions due either to inflammatory swelling and edema or carcinomatous infiltration or both The rugae about a benign ulcer tend to converge or radiate in a star like fashion, whereas in a carcinomatous ulcer they may be abruptly interrupted Benign craters are usually smooth or slightly irregular whereas malignant craters tend to be ragged and markedly irregular, but exceptions of both types occur And last, but not least, under suitable therapy the crater of the benign ulcer diminishes rapidly in size and disappears completely whereas carcinomatous craters decrease slightly and very rarely disappear completely—assuming a careful examination and reliable technic

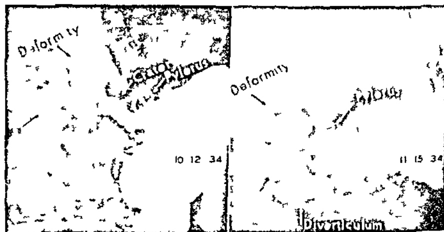


Fig 69—Marked deformity of both curvatures of a large duodenal bulb although the lumen is still quite adequate Between the pylorus and the deformity the duodenal bulb is rather ballooned out, producing a diverticulum like appearance The crater is usually found at or just proximal to the deformity In this case the crater is immediately beyond the pylorus (left view) A month later no evidence of crater was found although the deformity persisted The patient Unit No 103205 a male forty years of age had "stomach trouble of the classic ulcer type for ten years

The *gastroscopic interpretation* like the x ray is of great differential value in skilled hands but it is not infallible The benign ulcer according to Schindler ' is generally crater like rarely shallow, its floor is whitish yellow not often brownish in color although after an acute hemorrhage it may be dark red its edges are sharp often partly undermined The adjacent mucosa in early lesions is often normal later there may be marked inflammation of the surrounding mucosa but rarely of the entire stomach Converging folds occur The carcinomatous ulcer however is characterized by less sharp edges so that the ulcer floor seems to blend with the mucosa The floor is irregular and contains nodules nodes or ridges *It is* occa

sionally whitish or yellowish in color but more frequently brown brown red violet gray or a dirty color The malignant ulcer is usually elevated and appears to lie on a hill thus differing further from the benign ulcer The adjacent mucosa may be nodular'

The various criteria outlined must be carefully evaluated in the consideration of any given case The evidence may be sufficient to justify either a definite or a presumptive diagno is of neoplasm and hence to indicate treatment as such or it may be adequate to warrant a tentative diagnosis of a benign ulcer and provisional medical management but conclusive clinical proof that the lesion is benign is obtained only by the roentgenologic and gastroscopic demonstration of complete healing A sharply circumscribed penetrating lesion of the lesser curvature occurring in a stomach known to secrete acid gastric juice may be treated medically if its course is carefully studied Relief from pain and gain in weight are to be expected and in themselves are not very reassuring but continued distress may be significant The occult blood should disappear from the stool in two or three weeks if the lesion is benign and should continue if it is malignant but exceptions occur If roentgenologic and gastroscopic studies made at weekly or biweekly intervals show that the crater is decreasing rapidly in size and if it appears benign medical treatment may be continued in the expectation that complete healing will be demonstrable within a few weeks If on the other hand it changes very little or appears to be malignant a presumptive diagnosis of carcinoma should be made and subtotal gastrectomy be carried out if possible without further delay

Prognosis —The prognosis in peptic ulcer is excellent for the immediate attack but poor for the future in that recurrence is the rule The course of the disease is characterized by remissions and exacerbations The cures for peptic ulcer are therefore infinite in number for it is very easy to be misled by the therapeutic fallacy and draw the erroneous post hoc ergo propter hoc conclusion

Treatment —*General Considerations* —The therapy of peptic ulcer is essentially medical surgery if indicated is usually undertaken for the complications of ulcer less frequently for the lesion itself The problem may be divided into two distinct phases first the healing of the ulcer and second the prevention of recurrence On the whole the former is accomplished very much more easily than the latter In fact healing frequently occurs spontaneously Medical treatment cannot actually heal an ulcer it can only endeavor to create the best possible conditions for the process of healing and thus facilitate it Nature heals the ulcer Complete healing exists only when the defect is closed and covered with a normal glandular mucosa It is not possible for the clinician to know when this has occurred but obviously it is at least many weeks after the disappearance of pain of occult blood from the stool and the vanishing of the roentgenologic crater Treatment should therefore be continued for several months

A further reason for prolonged treatment is the recognized tendency of ulcers to recur at the same site or a different site even after complete healing has taken place and regardless of the type of medical or surgical treatment employed

Rest is essential in the treatment of many diseases in ulcer it is very valuable but often difficult to obtain The rest should be if possible both physical and mental the latter being even more important than the former Occasionally a strenuous hunting or fishing trip proves more restful than a period of bed rest Vacations often bring clearer perspectives and better attitudes

Psychotherapy is essential As a rule the superficial psychotherapy and encouragement incident to the medical program to be outlined is adequate Frequently sedatives such as phenobarbital and sodium bromide are of value In certain cases formal psychiatric care perhaps including detailed and prolonged psychoanalysis may prove helpful but unaccompanied by other medical treatment it is not adequate therapy even though a remission of symptoms ensues

Hospitalization with proper management is usually preferable to a vacation in the treatment of ulcer Meticulous attention to the detailed program of therapy to be described not only creates the best conditions for the healing of the ulcer but it is of

great psychotherapeutic value in establishing *the patient's confidence in himself*, in his treatment and in his doctor. In the hospital the patient learns that his condition is not unique, that the program of treatment can be carried out and learns how to do it. Two weeks of hospitalization or of rest in bed at home is usually the minimum period permissible. In difficult cases, a month or six weeks may be much more satisfactory, and occasionally a period of six months is desirable. Bathroom privileges may be allowed. The course of the lesion during this time should be determined at intervals by roentgenologic or gastroscopic studies. If possible, the patient should be kept away from work until the crater has disappeared. He must understand that he is confronted with a twofold problem: the healing of an ulcer and the prevention of its recurrence, and that certain restrictions and regulations of his life will be in order for an indefinite period, perhaps for life.

Acid Neutralization.—RATIONALE.—Sippy was the first to develop a program of therapy based on the premise that "the greatest known hindrance to the healing of peptic ulcer that is amenable to medical or surgical control ... is the disintegrating and digestive action of the gastric juice." Once this is removed, "Nature ... fills in the defect with granulation tissue and cicatrization of the ulcer may occur approximately as rapidly as it does elsewhere on other surfaces of the body." Sippy considered "peptic activity" to be the deleterious agent and attempted to neutralize the hydrochloric acid in order to inactivate pepsin. It is now known that the acid itself is more destructive than the pepsin, but in all other essential respects the extensive investigations of the subject carried out in the past two decades have corroborated the original concept of Sippy. If it were possible, practical and feasible to bring about complete and permanent gastric anacidity, there would be no ulcer problem. Unfortunately, there is no satisfactory method of attaining this goal. The Sippy treatment "aims however at 'maintaining an accurate neutralization of all free hydrochloric acid during the time that food and its accompanying secretion are present in the stomach.'" This goal also is somewhat difficult to attain and the continued secretion of acid gastric juice during the night is even more difficult to control than Sippy appreciated. Nevertheless, the rationale of the program is valid and it will be presented with the modifications indicated as the most practical and satisfactory type of management.

Neutralization of the acid gastric juice is maintained by means of the acid combining power of food proteins and by the acid neutralizing capacity of various types of alkali. It is important to point out two facts: first, that all foods and liquids when ingested stimulate the secretion of gastric juice, water being one of the most effective, and second, that the slight quantitative differences in secretion induced by various foods as worked out by Pavlov, are not of much practical importance. Fats inhibit gastric emptying and secretion, but this factor is not as important in maintaining neutralization of the gastric content as is the acid combining property of protein food. Furthermore, neutralization of the acid seems to accelerate gastric emptying more than the presence of fat inhibits it. The milk and cream mixture is used for its neutralizing value and because the added nutritive value of the fat in the cream is important.

DIET.—The customary schedule consists of the administration of 90 cc. of equal parts of whole milk and 18 per cent cream hourly from 7 A. M. to 7 P. M. The caloric intake and the taste may be modified as desired by increasing the hourly milk and cream feeding, by adding malt or chocolate syrup or by substituting whole milk or even skim milk for the milk and cream. A gain in weight is usually desirable. Many patients state they are unable to take milk or milk and cream, but very, very few indeed are actually unable to do so.

Small additional feedings may be given with or substituted for the milk and cream beginning on the first day of treatment or begun a few days later. A good program is to begin with one feeding on the second or third day and add one every other day until six are being given. It is well but not absolutely necessary to restrict the foods for the first three feedings to the following:

Cream of Wheat, Farina, Boiled rice, soft cooked egg, cream or custard or cornstarch pudding, jello, ice cream.

Orange juice and other fruit juices may be given as desired and often help to relieve the initial distaste for milk and antacid

When four feeding are reached the following may be added

Toast, crackers creamed soups (strained) plain cake soft-cooked egg

The gradual increase in the additional feedings has a definite psychologic value in that it enables the patient to see progress from day to day and gives him something to which to look forward In some instances particularly in moderate obstruction the six feedings may be too much and a three feeding schedule may be maintained to advantage for several weeks provided the caloric intake is adequate Ordinarily the patient will be ready some time in the third week to begin the so called three meal program' the hourly schedule of which is as follows

8 00 Breakfast
8 30 Powder
9 00 Milk and cream
9 30 Powder
10 00 Milk and cream
10 30 Powder
11 00 Milk and cream
11 30 Powder

12 00 Dinner
1 00 Powder
1 30 Powder
2 00 Milk and cream
2 30 Powder
3 00 Milk and cream
3 30 Powder
4 00 Milk and cream
4 30 Powder
5 00 Milk and cream
5 30 Powder

6 00 Supper
7 00 Powder
8 00 Powder
9 00 Powder
9 30 Aspirate stomach
Record amount and reaction

The following diet may be used

BREAKFAST

1 Serving of
Fruits
Orange juice
Peach puree
Applesauce
Baked apple (no skin)
Prune puree
Pear puree
Apricot puree

Cereals
Cream of Wheat
Oatmeal (well cooked)
Boiled rice

Egg (1 or 2)
Soft boiled
Soft poached
Scrambled with milk and butter

1 or 2 slices of toast and butter

1 cup of coffee
1 cup of tea
1 cup of Sanka
1 cup of chocolate

Cream and sugar as desired

DINNER

Soups (strained cream soup)
Rice
Pea
Potato
Celery
Spinach
Lettuce
Asparagus
String beans
Tomato
Carrots

1 Serving of
Baked potatoes
Mashed potatoes
Rice
Spaghetti
Macaroni
Noodles
White or whole wheat bread rolls or biscuits

Vegetables strained or pureed or cooked until soft
Carrots
Peas
Beets
Squash
Asparagus
Spinach
Green beans

Meat 1 small serving of
Roast chicken
Stewed chicken
Broiled whitefish
Scraped beef
Minced beef or diced beef with gravy
Small portions of roast
Lamb
Beef
Mutton
Broiled steak and lamb chops may be taken after two or three months if thoroughly masticated

Desserts

1 Serving of
Bavarian cream
Lemon sponge
Grape sponge
Blanc mange
Cornstarch pudding
Tapioca custard
Vanilla custard
Ice cream
Sponge cake
Angel cake
Lady fingers
Arrowroot cookies
Vanilla wafers
Plain cake
Jello with whipped cream
Caramel custard
Cheese

SUPPER

Cream soup (see noon list)
Rice *or*
Cream of Wheat *or*
Soft egg

Crackers o
Buttered toast

Desserts (see noon list)

The diet consists of a fairly generous breakfast with dinner at noon and a light supper not exceeding 400 or 500 cc in total bulk The average caloric and vitamin intake on the three-meal ulcer management program is adequate, but additional supplementary vitamins may be prescribed if desired The patient is expected to follow the program outlined for a year or more reporting to the office or clinic at approximately monthly intervals for such changes as may be needed for x ray examinations or for other subsequent studies as indicated

ANTACIDS —Alkalis of various types especially calcium carbonate have been used in the treatment of indigestion from time immemorial The standard Sippy powders for many years consisted of (*a*) sodium bicarbonate (2 0 Gm) combined with calcium carbonate in doses of 0 65 1 3 or 2 0 Gm and (*b*) heavy magnesium oxide (0 65 Gm) and sodium bicarbonate 0 65 Gm These powders have excellent neutralizing value The calcium and sodium bicarbonate powders are the basic ones administered the magnesia powders being substituted for them only as needed for the regulation of the bowels Some patients do not require any magnesia powders others require three four or more If too many are given diarrhea and abdominal cramps ensue if too few are taken fecal impactions in the rectum or sigmoid may result Various other alkalis may be used The soluble sodium bicarbonate is much more likely to produce alkalosis than are the less soluble salts such as calcium carbonate tribasic calcium phosphate magnesium trisilicate or aluminum hydroxide Preference should be given to calcium carbonate (2 0 Gm doses), tribasic calcium phosphate (4 0 Gm doses) and magnesium oxide (0 5 or 1 0 Gm doses) Aluminum hydroxide must be used in rather large amounts (30 cc doses) if satisfactory neutralization is to be maintained

The alkali should be given hourly from 7 30 A M to 7 30 P M and at 8 00 8 30 and 9 00 P M If desired it may be combined with the milk and cream at hourly intervals It is not sufficient to prescribe one to two doses after each meal The hourly dose required varies with the preparation used The effectiveness of the amount used in each case may be checked by determining the degree of neutralization in the gastric content obtained in samples aspirated at various times during the day A good routine procedure is a daily aspiration at 9 30 P M and a sampling at 4 00 P M., three to four times a week Considerable difference of opinion exists with regard to the hydrogen ion concentration optimum for the healing of ulcer, for many lesions heal in the presence of acid gastric content There is evidence however that the best conditions obtain when the pH is above 4 0

ASPIRATION OF THE STOMACH —The routine gastric aspiration at bedtime is important because the emptying of the stomach decreases the period during which the ulcer is exposed to the action of the acid gastric content When the aspiration is performed approximately thirty minutes after the taking of a powder the aspirate should contain no free acid if the dose of alkali is adequate If the stomach empties rapidly however the powder may be discharged into the duodenum in a few minutes and the stomach then secretes the 20 to 40 cc of clear and highly acid gastric juice subsequently aspirated The aspiration also has the psychologic effect of reminding the patient that the evening meal should be small and that his definite regimen should be carefully followed The patients as a rule quickly become accustomed to the procedure learn the technic and are able to continue the aspirations for months if necessary until the quantity obtained regularly does not exceed 50 to 100 cc As a rule aspiration is not so important in gastric ulcer or in nonstenosing duodenal ulcer as it is in pyloric or duodenal lesions with marked narrowing of the channel but occasionally nonobstructive lesions are associated with retention due presumably to pylorospasm hypertrophic stenosis of the pylorus or to some disturbance in the reflex opening mechanism

CONTROL OF THE NIGHT SECRETION —In patients with gastric and more especially in those with duodenal ulcer the stomach usually continues to secrete rather large quantities of highly acid gastric juice for the first few hours during the night a fasting so called night secretion definitely greater than the fasting secretion of the otherwise normal stomach It is not due to the milk and cream and alkali administered during

the day for it occurs without such a program This excessive continued night secretion constitutes a hindrance to healing occasionally prevents healing and is difficult to control The administration of 0.5 to 1 0 mg of atropine sulfate by mouth at 6 00 P M and again after the evening aspiration is helpful Rather rarely additional doses (2 0–4 0 Gm) of calcium carbonate at 10 00 P M midnight 2 00 A M 4 00 A M and 6 00 A M may be in order In very rare cases the milk and cream schedule may be continued through the night or a continuous drip therapy be used

CONTINUOUS DRIP THERAPY —The administration of food or antacid or both by means of a continuous drip through a nasal catheter has certain advantages as well as disadvantages The feeding is in effect a fistula feeding thus eliminating the very important cephalic phase of gastric secretion The Winkelstein formula consists of 1 liter of milk containing 5 Gm of sodium bicarbonate every eight hours Very satisfactory neutralization can be maintained throughout the day and night It is as a rule not feasible to continue this procedure for more than a week or two after which a careful program should be followed The disadvantage consists chiefly in the discomfort induced by the presence of the nasal catheter the difficulty of adjusting the drip properly the dryness of the throat and the possible greater frequency of pulmonary complications

Complications of Antacid Therapy—ALKALOSIS —The term "alkalosis is applied to an alteration of the electrolytes of the blood serum characterized by an elevation of the carbon dioxide content and the pH It may be produced by the administration of soluble alkali (sodium bicarbonate) in which case there is also an elevation of the fixed base (sodium) in the serum or by depletion of chloride (low intake of salt vomiting aspiration of the stomach) in which case the fixed base of the serum is not elevated but is in fact lowered Since sodium bicarbonate is no longer prescribed as an antacid the first type of alkalosis is seen almost exclusively in individuals who have acquired the baking soda habit The second type is seen in patients with continued vomiting from obstruction at the outlet of the stomach both benign and malignant and in patients receiving (*a*) a low intake of chloride and (*b*) routine nocturnal aspirations of the stomach

In both of these types of alkalosis the kidney is not primarily involved even though there is a rise in the blood urea nitrogen and a decrease in renal function The initial symptoms of alkalosis consist of loss of appetite with distaste for the milk and cream and powders Nausea and vomiting may ensue Weakness and lassitude may be marked often accompanied by a dull headache and slight clouding of the sensorium Tetany is rarely seen Moderate chemical alkalosis is frequently present without symptoms

TREATMENT consists of the discontinuance of soluble alkali if this is being given and of the administration orally or parenterally of large amounts of fluid and sodium chloride —3000 to 4000 cc of normal saline daily by hypodermoclysis or intravenously or an equivalent amount by mouth An additional 5 to 10 Gm of sodium chloride may be given orally in the form of pills or capsules As a prophylactic procedure 3 to 5 Gm of sodium chloride may be added to the daily ration of milk and cream

BOWEL DISTRESS —Abdominal distress during ulcer management is usually attributable to a functional disturbance resulting from improper regulation of the bowels The powders and the diet should be manipulated in such a fashion as to produce daily formed stools

FECAL IMPACTIONS —Special attention must be given to regulations of the bowels to prevent the formation of rectal or sigmoidal impactions of feces This is best accomplished by alternating the calcium and magnesium powders until a mild diarrhea is produced and then determining just how many magnesium powders are required to maintain normal bowel function When impactions form they must be broken up digitally at once and removed manually or with large enemas At times the rectum is found filled with soft putty like material which the patient is unable to expel The enemas and rectal examinations should be continued until the rectum is proved to be empty In rare instances a large calcium stool may lodge in the sigmoid and the clinical picture

of paralytic ileus develops Watchful waiting with the application of hot stupes or an electric pad to the abdomen and if necessary the use of a Wangensteen or Miller Abbott tube for the relief of the nausea vomiting and distention, is rewarded in a day or two by the passage of the stool into the rectum at which time it can be removed manually Warm oil retention enemas may be helpful but repeated large water or soapsuds enemas are likely to produce further distention of the abdomen without bringing the fecal mass down into the rectum

RENAL AND URETERAL CALCULI —There is no satisfactory statistical proof that this complication is seen in greater than the normal frequency in patients receiving antacid therapy Theoretically and practically there seems to be no contraindication to the use of the nonabsorbable salts of calcium magnesium and aluminum

ACUTE APPENDICITIS —This complication of antacid therapy is seen so frequently that the possibility must always be considered although statistical evidence that it occurs in greater than the anticipated frequency does not exist

Inhibitory Drugs —ATROPINE and SIMILAR DRUGS are commonly used in the treatment of ulcer presumably as antispasmodics but it is difficult to prove that they lessen pylorospasm or spasm at the site of the ulcer They do inhibit to a certain extent however both gastric peristalsis and gastric secretion and make possible neutralization of gastric acidity with smaller amounts of alkali than would be needed without them Atropine is as satisfactory as any of the antispasmodics The maximum total daily dose tolerated is usually 1 0 to 1.5 mg and does not exceed 2 0 or 3 0 mg dryness of the mouth blurring of vision and toxic psychosis being not uncommon with large daily doses (3 0 mg or more) Since the evening and night secretions are the most difficult to control the atropine is used most effectively perhaps if given in the afternoon at 4 or 6 P M and at bedtime

X-ray Therapy —Radiation therapy is helpful in certain cases not as a stimulant to the healing of the ulcer for there is no evidence that the x ray ever directly stimulates the process of tissue repair but as a means of inhibiting gastric secretion and thus facilitating healing The radiation should be directed at the fundus of the stomach The effect on secretion is variable and as a rule not permanent If a phase of complete achlorhydria is produced partial or complete healing invariably occurs, the degree depending apparently on the reparative ability of the tissue and the duration of the achlorhydria

Hormone Therapy —Enterogastrone a hormone prepared from duodenal mucosa and certain extracts of pregnancy urine normal female urine and male urine exert a definite inhibitory effect upon gastric secretion but these substances are not yet available in sufficient quantity for extensive clinical trial

Foreign Protein Therapy —Foreign protein therapy has no rational basis in the treatment of ulcer except the psychotherapeutic as illustrated by the excellent results ' obtained by the intravenous injection of distilled water

Foci of Infection —These should be removed for local reasons a remission of symptoms may follow their removal but there is no evidence that the relationship is causal

Complications — *Perforations* — ACUTE PERFORATION —Acute perforation is the most dangerous complication of peptic ulcer and accounts for 65 to 85 per cent of the deaths from this disease The duodenum is the site of the perforation nine times more frequently than the stomach The accident occurs forty nine times more often in males than in females An ' ulcer history is present in from 60 to 75 per cent of the cases

DESCRIPTION —Moynihan s description of the clinical picture is superb The picture is so characteristic that error is hardly possible I have had the opportunity of seeing three patients within five minutes of this terrible catastrophe and so deep an impression was made upon me that the recollection is a haunting one For the agony suffered by the patient is almost beyond belief and is written on every line of a face that speaks of torture The face is pale haggard anxious and appealing the eyes wide and watchful the brow and temples bathed in sweat the hair soaked The patient struggles for breath in short panting respirations which are wholly costal for the diaphragm

being an abdominal muscle is fixed Words spoken are jerked out in expiration only every syllable is part of a deep moan What strikes every onlooker is that the patient s body is rigid and motionless no slightest movement dare be attempted If an en deavor is made to touch the abdomen the patient s hands are at once lifted in protest and in protection but the chest and abdo men stay motionless When examination is made it is realized at once that the patient is cold and the temperature will rarely be found more than 95° or 96° F The abdomen is immobile and the muscles are taut and rigid hard as a board it is said but if there is anything harder it is the abdomen in this time of catastrophe A further examination of the abdomen will almost always show an area of greater tenderness and if possible of added rigidity over the area involved in stomach or duodenum

When the pulse is examined a great sur prise is felt for it is not increased in fre quency nor diminished in volume blood pressure is not diminished and in a few cases that we have examined the blood volume is unchanged There is therefore no shock Great harm has come from the almost in variable use of the word shock to describe the conditions The use is really inde fensible and indeed dangerous When a pa tient is seen whose general and local condi tions suggest the occurrence of a catas trophe and the pulse is found to be normal the practitioner is betrayed for he has learnt that among the symptoms of rupture is shock' and shock being absent the diag nosis is impugned or denied Shock is never a symptom of perforation It is a symptom of peritonitis which follows quickly upon leakage from the stomach or duodenum In the patient s interest no less than in the service of truth we must discharge the word shock from its use in this connection

The period of initial profound prostra tion varies in different patients and may be ascribed to variations in the size of the per foration the character of escaping contents —especially in respect to acidity—the gen eral condition of the patient and so forth Within an hour or two it is followed by a period of reaction characterized by an improvement in the appearance of the pa tient pallor being replaced by flushing lines of anxiety being smoothed away, and the body growing warmer But the pulse stead ily rises the rigid abdomen becomes fuller and since the diaphragm is being pushed higher respirations become shallower For reasons which I gave many years ago fluids leaking from the stomach tend to trickle down to the right iliac fossa and to over flow into the pelvis So there may be acute pain or tenderness in the right iliac fossa and a careless diagnosis of appendicitis may be made It is in this stage that the absence of liver dullness upon which so high a value has long been placed will be recognized It is almost valueless I very rarely percuss the abdomen and I have been amused to see the liver percussed when it could be felt! At this time too vomiting may first be no- ticed and from now onwards conditions suf fer a fast and progressive deterioration

It is however the earliest stages of per foration for which we should be on the alert And remembering what has been said we may conclude that perforation of an ulcer in the stomach or duodenum is almost invari ably preceded by the history of a chronic ulcer and that some exacerbation of symp toms may have been observed in a few pre- ceding days When perforation occurs the patient is struck motionless he endures a degree of agony that reaches the very limit of human power to withstand his face is sweating he pants and groans on expira tion as he tries to speak His abdomen is inflexibly and unalterably rigid His pulse is normal No more need be said These signs and symptoms are compulsion enough for any medical man to say that Here is a grave abdominal catastrophe that cannot be treated except by surgery and to enlist the earliest possible help of the surgeon

If operation is not performed generalized peritonitis usually ensues the abdomen loses its boardlike character but not its rigidity or tenderness it becomes distended the pulse becomes gradually rapid weak feeble the respirations become more rapid and shal low Hippocratic facies appear and the pa tient dies the typical peritonitic death in the course of two to five days

Differential Diagnosis —The differen tial diagnosis of acute perforation is rarely difficult Biliary renal and intestinal colic lack the boardlike rigidity Perforation of

the gallbladder, however, is usually indistinguishable from that of the stomach or duodenum except for the fact that it typically occurs during or after the apparent subsidence of an attack of acute cholecystitis In coronary thrombosis not only is the rigidity absent but usually there is some radiation of the pain to the precordium sternum neck or arms In lobar pneumonia the temperature is elevated the respiratory rate is increased and the normal pulse to respiration ratio of 4 to 1 is decreased to 3 or 2 to 1 In the gastric crisis of tabes dorsalis the abdominal rigidity is absent Argyll Robertson pupils are usually present The onset of acute appendicitis is less sudden the rigidity is less intense the tenderness is most marked over McBurney s point In mesenteric occlusion and intestinal obstruction the pain is rhythmical intermittent and the rigidity less intense In ruptured ectopic pregnancy the pain and tenderness are in the lower abdomen and the rigidity is only moderate

The most difficult differentiation is that of acute pancreatitis If the patient is a female the diagnosis of acute pancreatitis is much more probable because 98 per cent of acute perforations in peptic ulcer occur in the male Disease of the biliary tract is usually present in acute pancreatitis but there may be no history of biliary colic Marked shock is almost always present The abdominal rigidity is not so intense or widespread nor the tenderness so complete Jaundice of slight degree is present in about one half the cases and often at an early stage the patient develops a characteristic slate blue tinge of color seen most distinctly in the lips in the lobes of the ears in the face and in the fingernails The urinary diastase the fasting blood sugar and the glucose tolerance curves are elevated in some cases Extreme gaseous distention of the stomach and colon (meteorism) may be observed

TREATMENT —The urgent and immediate indication in acute perforation is immediate operation Spontaneous closure does occur but operation should never be deferred in the hope that it may take place The earlier the operation the better the prognosis for few die if the operation is carried out within ten or twelve hours Rarely when the patient is first seen several hours after the onset of symptoms and from the rapid subsidence of the pain the sharp localization of the tenderness and rigidity and the excellent condition of the patient it is apparent that spontaneous closure has already occurred surgery may be deferred and the patient treated by starvation for two or three days before instituting ulcer management In the vast majority of cases however operation should be performed at once The perforation should be closed by suture and no further procedure carried out unless it is evident that the suturing has produced marked stenosis in which case a gastroenterostomy should also be performed Some surgeons prefer to carry out an initial primary subtotal gastrectomy but the mortality rate is higher

In *subacute perforation* the clinical picture is similar but less intense Spontaneous closure of the defect may occur as a result of fibrinous adhesions to omentum liver pancreas or other structure and recovery ensue without surgical interference These so called formes frustes perforations are more frequent than is generally recognized but this fact does not justify failure to operate when acute perforation is diagnosed or suspected In some cases of perforation, even though spontaneous closure takes place abscesses develop about the ulcer or the infection extends to form a subphrenic abscess

In *chronic perforation* the base of the ulcer is usually formed by the capsule of the pancreas or liver rarely is the parenchyma of these organs attacked Chronic perforation is of very little clinical significance except when a gastrojejunocolic fistula is produced

In *peptic ulcer of the esophagus* perforation of an acute subacute or chronic type may take place into the mediastinum pleura or pericardium

Massive Hemorrhage — DEFINITION — Massive hemorrhage may be defined as the vomiting of gross blood or the passage of tarry stools The bleeding may be of all grades of severity from the 60 cc required to give a tarry stool without symptoms to several hundred cc resulting in severe collapse and even rapid death

MORBID ANATOMY —Fatal hemorrhage is almost invariably arterial in origin the pan

creaticoduodenal the gastric coronary or one of their main branches being eroded

INCIDENCE.—Probably 20 to 25 per cent of all patients with peptic ulcer experience massive bleeding at some time or other

The MORTALITY RATE varies from 1.5 to 20 per cent or higher It rises with age, being at least four times higher in patients over fifty than it is in patients under fifty It does not rise materially with recurring hemorrhages

MELENA NEONATORUM or hemorrhage in the newborn deserves separate mention for in about 50 per cent of the cases it is due to peptic ulcer The symptoms appear on the first day of life never later than the fifth day and the deaths all occur within the first two weeks (Hurst Theile)

SYMPTOMS AND DIAGNOSIS.—Since peptic ulcer is the most frequent source of hemorrhage in the digestive tract it should be suspected in every case regardless of the presence or absence of pain In gastric ulcer hematemesis is usually present as well as melena in duodenal ulcer it occurs in about one fourth of the cases The patients usually give a history of epigastric distress of the ulcer type but there may be no distress whatsoever at the time of hemorrhage or indeed previously

The symptoms consist of faintness weakness dizziness headache perspiration thirst dyspnea syncope and collapse the severity depending largely upon the suddenness and severity of hemorrhage and the resultant rapid drop in blood pressure Usually the vasomotor system regains its tone rapidly and the blood pressure rises but in severe hemorrhage it remains low usually below 100 often 90 mg of mercury the pulse more or less gradually increases in rate and the patient continues in shock The more marked and persistent the drop in the blood pressure and the more rapid and weak the pulse the greater is the danger In the first few hours the blood count may be normal except for the moderate leukocytosis of hemorrhage The drop in the red cell count and in the hemoglobin appears later as the total blood volume is restored by dilution A moderate azotemia occurs due to the absorption of protein from the blood in the intestine the dehydration and to decreased renal function as a consequence of the drop in the blood pressure with the resultant diminished blood flow through the kidney

PROGNOSIS.—Recovery is the rule but death may occur at any time usually two to five days after the onset of symptoms and results either from exsanguination or from intercurrent complications such as pneumonia or perforation

TREATMENT.—The time honored therapy in massive hemorrhage is bed rest elevation of the foot of the bed application of an ice bag to the epigastrium morphine in doses adequate to quiet the restlessness and complete starvation for several days In recent years the frequent feeding program of Meulengracht has again called into question the wisdom of starvation The following program based essentially on that used and recommended by Sippy has been found superior to routine starvation and is thought to be at least equal to the Meulengracht procedure

Absolute rest in bed should be maintained and restlessness controlled by the use of *morphine* 1/8 1/6 or even 1/4 of a grain every four hours combined with *atropine* sulfate 1/120 1/100 or 1/75 of a grain The patient should not be snowed under The blood pressure and the pulse rate should be watched carefully readings being taken at hourly or half hourly intervals The blood count does not usually drop until several hours after the initial hemorrhage and hence is not as good an index of the severity of the bleeding as are the blood pressure and the pulse rate

Blood transfusion is indicated when the pulse rate exceeds 120 per minute and the blood pressure drops below 90 or even 100 mm of mercury When the bleeding takes place slowly and continuously the pulse rate and blood pressure may not reach these levels and yet transfusion may be indicated because of the anemia If the erythrocyte count is below 3 000 000 cells per cubic millimeter transfusion is desirable if it is below 2 000 000 cells transfusion is imperative Many patients recover spontaneously from such levels but their margin of safety is very narrow and a relatively small hemorrhage may prove fatal The blood should be matched most meticulously Each transfusion should consist of 500 or 600 cc of whole blood and as many should be given as

necessary The greater the number of transfusions required the graver the prognosis, not because the transfusions are harmful but because the great need for them constitutes evidence that a large and probably sclerotic vessel is the source of the bleeding

Starvation is indicated only if the patient is vomiting in which case it should be continued until this has subsided and the patient desires food Dryness of the mouth may be relieved by cracked ice and by the daily subcutaneous (*not* intravenous) administration of small amounts (1000–1500 cc) of normal saline with or without glucose Occasionally, if the lesion, from previous x ray examinations, is known to be duodenal and accompanied by considerable stenosis, starvation may be combined with continuous aspiration of the stomach through a Wangensteen tube A surprising amount of highly acid gastric juice may be obtained If the bleeding ceases promptly the procedure may be continued

Feeding and antacid ulcer management is in the absence of vomiting preferable to starvation Milk and cream in equal parts or whole milk may be given in amounts varying from 30 to 120 cc usually 90 cc hourly from 7 00 A M to 10 00 P M and at two hour intervals through the night Calcium carbonate, 2 0 Gm should be given hourly from 7 30 A M to 9 30 P M or on the hour with the milk and during the night with the milk in 4 0 Gm doses wakening the patient if necessary A sufficient number of powders of magnesium carbonate in doses of 2 Gm, usually totaling 2 to 10 Gm daily, must be substituted for the calcium carbonate to *prevent rectal impactions*

This program is continued until the stools have been negative for occult blood by the benzidine test for at least two or three days and until the patient s general condition is good at which time roentgenologic and gastroscopic examinations are in order to determine the location nature and extent of the lesion and the complications present Aspiration of the stomach may then be carried out safely If the occult blood in the stool does not disappear in the course of two or three weeks and if the patient is in good condition, the x ray examination should not be further deferred The risk of the procedure, if carefully carried out, is small, and it may be found that the bleeding lesion is not a benign ulcer, but a frank neoplasm or varices of the esophagus

Surgical treatment may be indicated in certain cases Usually by the time the need for ligation of the artery has become apparent the patient has become a poor operative risk and hence surgical intervention is further deferred It may be difficult to find the bleeding vessel at operation and to deal with it adequately if found There is evidence that immediate surgical treatment employed routinely in all cases of hematemesis and melena would increase rather than lower the mortality rate On the other hand it may be possible to select the patients with rapid continued bleeding and to lower the mortality rate in these cases by surgical treatment Gastro enterostomy alone is not effective The bleeding vessel must be ligated Subtotal gastrectomy may be advisable In patients with recurring massive hemorrhage subtotal gastrectomy may be indicated after recovery as a prophylactic against further bleeding although ulcer and massive hemorrhage do recur after this type of therapy as well as after other forms of medical and surgical treatment Nevertheless the incidence is low and hence subtotal gastrectomy may in certain cases be chosen as the best procedure

Acute Perforation and Massive Hemorrhage—These are as a rule independent complications of peptic ulcer About 10 per cent of the acute perforations occur in patients who have experienced massive hemorrhage Occasionally the two complications occur within a few days of each other After recovery the ulcer may recur and either complication ensue

Obstruction—DEFINITION—The term obstruction" referring to obstruction to the passage of food from the stomach *to the* intestine is loosely used It is often applied to persistent vomiting or the vomiting of food eaten the previous day or the *failure* of the stomach to empty properly as evidenced by abnormal gastric retention *of a* food or barium meal The terms 'obstruction' and 'retention are thus *confused* they are not synonymous Retention may be present in the absence of *gastric disease* Obstruction *per se* may be due to spasm of

the pylorus to edema and inflammatory swelling about a pyloric or duodenal ulcer, to cicatricial stenosis, or to a combination of these factors The criteria of obstruction must therefore be critically evaluated to determine their significance

DIAGNOSIS —The mere retention of food or barium in the stomach for abnormal periods is not direct evidence of obstruction unless the retention be extreme If food is retained in the stomach for twenty four hours as may be demonstrated by the vomiting of food taken the day previously, obstruction is almost always present The presence of sarcinae and yeast in the gastric content betokens continued retention for many days or weeks and thus constitutes definite evidence of obstruction

X RAY affords on the whole the most valuable evidence of obstruction for it permits determination of the site of the lesion and usually of its nature and also discloses the site of the obstruction its nature and the degree of stenosis Pylorospasm although it may occur with an ulcer at any point in the stomach or duodenum is usually not very important unless the lesion is intrapyloric If the pyloric obstruction is due to a hypertrophic stenosis of the pylorus surgical relief will frequently be required Usually however the lesion is duodenal in location and the question to be answered is the degree of cicatricial stenosis present Often this cannot be settled until the initial spasm edema and inflammatory swelling have subsided after a few days or even a few weeks of treatment The lumen of the normal duodenal bulb has a diameter of 2 to 3 cm If this is decreased to 5 or 10 mm the stenosis is moderate if decreased to 2 to 4 mm the stenosis is marked and if the lumen is decreased to a hair line or to a diameter of 1 mm the stenosis is high grade usually accompanied by gastric dilatation ballooning of the antrum and hyperperistalsis The maximum width of the channel should be determined fluoroscopically not from the film for the film may be exposed at the moment the muscle is in contraction thus suggesting a much more marked stenosis than is actually present

TREATMENT —Obstruction is the most frequent *indication for surgical treatment* in peptic ulcer The term is a relative one as has been pointed out previously, and hence the indication is relative In general it is wise to try the effect of medical management for ten or fourteen days before arriving at a decision for Sippy s original estimate that in 85 per cent of the cases the obstruction is due to spasm or inflammation is approximately correct In general need for *surgical intervention* may be said to be definite when two or more of the following conditions are present continued vomiting before admission to the hospital, motor meal retention sarcinae or yeast in the gastric content a quantity of 800 to 2000 cc obtained at the bedtime aspiration rapid loss of weight on management gross peristaltic waves passing across the contour of the stomach from left to right and the x ray disclosure of a huge dilated stomach with hyperperistalsis but with little or no barium passing into the duodenum When the evening aspiration is only 300 or 400 cc and if the patient does not lose weight but even gains weight on treatment the indication for operation is much less definite

The *location* and the *nature of the obstruction* are important considerations In the case of the duodenal ulcer operation is definitely not indicated for obstruction if the maximum lumen through the deformity as seen roentgenologically is over 5 mm in diameter usually not if the lumen is over 2 or 3 mm in diameter and on the other hand usually is indicated if the maximum lumen is less than 2 mm in diameter The width of the channel usually persists relatively unchanged as the ulcer heals occasionally it increases rarely does it decrease In the case of intrapyloric or prepyloric ulcer the obstruction and retention may decrease rapidly under management or it may persist The retention occasionally seen with ulcers of the lesser curvature of the stomach and due presumably to pylorospasm disturbance of the neuromuscular reflex or associated hypertrophic stenosis of the pylorus may be very persistent and warrant surgical interference

Depending upon the surgeon and the conditions present the *operations of choice* for obstruction are posterior gastro enterostomy pyloroplasty and gastroduodenostomy although some surgeons prefer a primary subtotal gastrectomy The initial ulcers almost

invariably heal following operation the difficulty is to be found in their recurrence later, or rather in the development of new ulcers later at the new stoma or in the stomach Statistics on the *incidence of recurrent ulceration* vary roughly from 2 to 40 per cent Subtotal gastrectomy seems to result in a lower incidence of recurrence, although the initial mortality rate is higher A further disadvantage of subtotal gastrectomy is the fact that the jejunal ulcers which do occasionally develop after this operation are extremely difficult to treat medically and can be treated surgically only by further resection and at greater risk

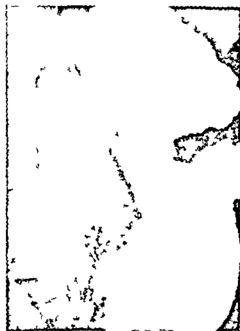


Fig 70—Hour glass contracture of the stomach secondary to gastric ulcer the ulcer being visible *en face* In this case the contracture was chiefly spastic for it disappeared almost completely as the ulcer healed The patient Unit No 130044 a female fifty two years of age had had intermittent epigastric distress for ten or twelve years Maximum free acidity 130 (histamine) The ulcer was repeatedly seen roentgenologically as its course to complete healing was followed but repeated gastroscopic examinations failed to disclose its presence, due presumably to the fact that it was located in a so-called gastroscopic blind area

Hour glass contracture of the stomach usually results from long standing chronic gastric ulcer although a type of hour glass deformity is seen in certain cases of carcinoma lues and diaphragmatic herniation It is a strange fact that hour glass contracture is eight or nine times more frequent in females than it is in males The ulcer is found healed at autopsy in about half the cases The incisura is sharp and narrow, involving the greater curvature almost exclusively and drawing it toward a point on the lesser curvature at which there may or may not be seen a penetrating ulcer of variable size usually rather small (see Fig 70) A bilocular or rarely a trilocular stomach results, seen much more clearly when the stomach is distended than when it is contracted. Rarely is the stenosis sufficient to be actually obstructive The contracture may involve the mucosa chiefly and hence not be apparent from the serosal surface

The history is as a rule, of many years duration the distress is mild vomiting massive hemorrhage or acute perforation may occur Not infrequently these patients give a history of a massive hemorrhage or an acute perforation in the second or third decade of life followed by many years of chronic indigestion Medical treatment usually suffices although occasionally the ulcer recurs with sufficient persistence or the obstruction is sufficiently complete to warrant operation

Jejunal Ulcer—With the exception of the uncommon ulcer of Meckel s diverticulum and the very rare primary ulcer of the jejunum associated with ectopic gastric mucosa peptic jejunal ulcer is a complication of gastro enterostomy

Incidence—Statistics vary greatly as to the incidence of the lesion some authors reporting it to be as low as 1 or 2 per cent, while others find it as high as 40 per cent. The latter figure is more nearly correct Ulcer develops in a certain number of cases irrespective of the type of gastro enterostomy performed irrespective of the type of anastomosis made and irrespective of the suture material used The lesion is said to be more frequent when an entero enterostomy is made in addition to the gastro enterostomy and is particularly frequent if a Roux Y operation is performed These clinical observations are in accord with the experimental studies mentioned in the section on etiology and pathogenesis Jejunal ulcer is definitely less frequent after subtotal gastrectomy than it is after gastro enterostomy alone and it is less frequent when the procedure is carried out for gas

the ulcer than it is when carried out for duodenal ulcer Jejunal ulcer practically never follows gastro enterostomy for gastric carcinoma

SYMPTOMS —The symptoms of recurrent jejunal ulcer resemble those of primary gastric or duodenal ulcer although the relationship of the distress to food taking is likely to be less definite and the pain usually is referred to the left mid abdomen or even to the left lower quadrant Massive hemorrhage occurs quite frequently Acute perforation is rare Chronic perforation is common particularly into the colon producing even without pain a gastrojejunocolic fistula and severe diarrhea

DIAGNOSIS —Recurrent abdominal distress in a patient with a gastro-enterostomy always suggests the presence of jejunal ulcer Usually the lesion can be demonstrated roentgenologically not infrequently it can be seen gastroscopically also

TREATMENT —Medical treatment is difficult If it is undertaken the course of the lesion should be followed closely by x ray and gastroscopy Surgical treatment is usually to be preferred and in the case of gastrojejunocolic fistula is imperative The gastro enterostomy may be simply undone provided the channel through the bulb is adequate A new duodenal ulcer may then develop If a second gastro-enterostomy is made at the time the first one is undone a new jejunal ulcer is likely to develop If subtotal gastrectomy is performed the mortality rate is somewhat higher than it is for primary resection and there is a fair likelihood of recurrence after resection for these are the so-called intractable cases of ulcer The treatment of jejunal ulcers developing after resection is most difficult Surgically the only available procedure is further resection Medically any or all measures may be tried complete healing may take place but recurrence is the rule It is important to know that in the intractable cases recurrences occur after both medical and surgical treatment Extreme care patience and perseverance must be maintained for many years It is perhaps in this group that intensive radiation therapy is most helpful

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DISEASES OF THE INTESTINES

DISEASES OF THE DUODENUM

Peptic ulcer is the most frequent affection of the duodenum It usually appears in the first portion the so called duodenal bulb, it occurs rather often at the junction of the first and second portions occasionally it develops in the upper part of the second portion of the duodenum and rarely as far down as the ampulla of Vater Lesions occurring beyond this point are not simple peptic ulcers (See Peptic Ulcer)

Duodenitis is a term applied to a non specific inflammation usually seen anatomically as a part of the erosive gastritis of Konjetzny a gastroduodenitis Clinically the diagnosis of duodenitis is made at times in patients who give a history of epigastric distress of the ulcer type and in whom the

roentgenologist finds a duodenal cap which fills and empties rapidly, seems 'irritable' and rather fuzzy in outline, but without definite deformity or crater formation Not infrequently in such individuals an ulcer crater or deformity is found months or years later It is probable that the process represents an early phase of the acid attack on the mucosa and that the basic problem therefore is that of peptic ulcer (See Peptic Ulcer)

Diverticula of the duodenum may be divided into those occurring in the bulb and those in the remainder of the duodenum The former are invariably secondary to peptic ulcer and do not cause symptoms Diverticula of the second, third and fourth portions are usually considered as congenital but the mechanism of their formation is not known they are usually found accidentally by x ray and bear no relationship to the symptomatology present unless as occurs very rarely they become the site of infection and inflammation

Carcinoma of the first portion of the duodenum is a great rarity scarcely more than a dozen cases having been reported in the medical literature of the world In the other portions of the duodenum however the lesion is not uncommon (See Intestinal Neoplasms)

Stricture of the duodenum may occur at any level most frequently in the first portion as a result of peptic ulcer Congenital strictures usually involve the second portion are often complete and cause the death of the infant within a short time unless recognized and treated surgically Extremely rare cases have been reported of incomplete congenital stricture discovered in adult life and producing intermittent attacks of nausea and vomiting Duodenal obstruction may be produced also by external adhesions such as those resulting from an adhesive tuberculous peritonitis severe cholecystitis, or neoplasm of the biliary tract

Duodenal stasis is a term applied to cases in which considerable to and fro churning or 'puddling of barium with reverse peristalsis is seen roentgenologically in the second portion of the duodenum It is a normal variant found most typically in lean lanky individuals with long abdomens It has been interpreted erroneously as a cause of symptoms diets belts and operations have been devised for it

Mesenteric duodenal ileus is a rare condition in which the third portion of the duodenum caught between the spine posteriorly and the mesenteric vessels anteriorly becomes partially or completely obstructed The duodenum is enormously dilated The symptoms are those of high intestinal obstruction with continued upper abdominal distress, nausea and vomiting and loss of weight

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VISCEROPTOSIS

(Splanchnoptosis Glenard s Disease)

This is a term applied to prolapse or falling of the various viscera It is not a disease entity but rather a manifestation of a lean lank body build with more or less relaxation of the abdominal wall The stomach and transverse colon may extend down to the brim of the pelvis Various symptoms have been ascribed to the condition belts have been devised for it as in duodenal stasis and operations even have been performed in attempts to elevate the various structures As a matter of fact there are only *two* organs which are ever affected seriously by ptosis (1) the kidney with resulting attacks of Dietl s crisis and (2) very rarely indeed the spleen which has been known to be-

come strangulated in the pelvis Otherwise visceroptosis may be disregarded

WALTER L PALMER

DIARRHEA

Definition —Diarrhea consists in the evacuation of watery or unformed stools It may be acute or chronic It is a symptom present in a great variety of disorders and diseases hence all cases should be studied carefully

Etiology —The numerous causes of diarrhea may be partially classified and listed as follows

- Enteric infections such as bacillary dysentery cholera, typhoid and paratyphoid fevers, food poisonings (usually staphylococcal) and parasites particularly *E histolytica*
- Food sensitizations particularly shell fish strawberries and eggs
- Poisons such as arsenic, mercury silver salts
- Avitaminoses particularly pellagra and sprue
- Toxic or septic states such as sepsis measles thyrotoxicosis Addison s disease chronic nephritis
- Circulatory disturbances secondary to cardiac decompensation or cirrhosis of the liver
- Emotional disturbances such as fear and grief
- Incomplete intestinal obstruction
- Non-specific infections such as regional enteritis and chronic ulcerative colitis
- Neoplasms of any type of the stomach pancreas or intestines

Symptoms —The clinical pictures seen in these different states vary a great deal particularly in severity and in duration but nausea and vomiting abdominal cramps tenesmus and frequent watery stools more or less characterize them all In the usual so called simple acute diarrhea the etiology is often not known and not discovered The attack lasts one to three days the stools vary from three or four to fifteen or twenty per day usually watery light brown or gray or green in color flaked with mucus and often with a very foul odor Blood is rarely present The intermittent cramps subside after the first day as does the vomiting The temperature is usually not elevated although it may rise 1 or 2° F rarely higher The leukocyte count is normal or slightly elevated In severe cases the prostration and collapse may be profound

Diagnosis —In simple acute diarrhea the diagnosis is made by the brief duration of the attack and by the failure to find a specific cause

Treatment.—In simple acute diarrhea, as in all diarrheas rest is of great importance It is well to keep the patient in bed and to give no food for the first twenty four hours Normal saline with 5 per cent glucose may be given if convenient subcutaneously or intravenously in amounts of 1000 to 1500 cc once or twice or even three times in twenty four hours depending on the degree of dehydration Hot water weak tea broth or barley gruel may be permitted in small amounts after the nausea and vomiting have subsided and if the patient has developed a real desire for food Boiled milk toast soft cooked eggs and custard may be given later Hot stupes may be applied to the abdomen although usually a hot water bottle or an electric heating pad is sufficient Atropine should be given in full doses 1/120 to 1/60 of a grain (0 0005 to 0 001 Gm) every four to six hours hypodermically When the pain is severe codeine sulfate 1/2 to 1 grain (0 03 to 0 06 Gm) or morphine sulfate 1/8 to 1/4 grain (0 008 to 0 015 Gm) should also be given as needed Paregoric and bismuth are of relatively little value Calomel a time-honored remedy is best avoided as is castor oil The irritating substance is usually removed by the diarrhea in a short time However castor oil causes such a complete evacuation of the colon that it is frequently followed by a cessation of bowel movements for one or two days Enemas or irrigations are not indicated The patient should be advised to rest and to adhere to a bland diet until the bowel function has been normal for several days

WALTER L PALMER

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CONSTIPATION

Definition —Constipation is defined as the passage of unduly hard and dry fecal material The consistency of the stool is more important than the frequency of defecation or the quantity expelled The average normal individual passes one well formed

stool of good caliber daily although people in the best of health may defecate only one, two or three times per week Patients have various notions about normal bowel function and constipation some expect a large watery stool after each meal the majority consider themselves constipated if more than twenty four hours elapses without a bowel movement Those who complain of constipation usually are not constipated in the sense of passing hard dry stools but rather in the sense of not passing the quantity of feces with the frequency they desire True constipation without abdominal distress is as a rule atonic whereas if abdominal pain or discomfort is present, the constipation is usually spastic or hypertonic

Normal Intestinal Motility—The motility of the normal digestive tract varies considerably The stomach empties in from two to seven hours Digestion in the small bowel takes place rapidly the time required for completion after food leaves the stomach not exceeding two to four hours The undigested residue enters the cecum in a liquid state The chief change occurring in the colon is the absorption of water Normally as the food residue traverses the colon its consistency increases so that a solid column is emptied into the pelvic colon from the descending colon The defecatory reflex is initiated by the presence of a fecal mass in the lower sigmoid and rectum

The rate of transit through the colon varies enormously usually requiring from one to three days but not infrequently requiring four or five days or longer If the progress is so rapid that the residue is evacuated before the proper amount of water has been absorbed the stool is unformed mushy or watery whereas if motility is slow too much water is absorbed and the stool is hard and dry Diarrhea is thus defined as the passage of unformed mushy or watery stools constipation as the passage of stools that are hard and dry The frequency of defecation is not of great significance perhaps the average individual expels one formed stool daily many normal persons have two or three formed stools daily and on the other hand occasional individuals habitually pass perfectly normal stools at intervals of two to seven days The moderate amounts of gas evolved in the colon are usually absorbed by the blood the quantity passed per rectum as flatus depends on the diet and on the rate the colon propels the gas along

Atonic Constipation—This relatively uncommon condition may be said to exist when without abdominal distress the fecal matter reaching the rectum is hard and dry Symptoms arise from difficulty in expelling the large hard stools Satisfactory bowel function can usually be obtained by including in the diet adequate amounts of the more laxative foods such as oatmeal for breakfast spinach and prunes daily two other vegetables and two fruits either cooked or raw fruit juices whole wheat bread honey and syrup Some cases are helped by one or two ounces of brewers yeast daily Mineral oil or other mechanical or chemical laxatives are usually not necessary but on the other hand in the absence of abdominal distress do little harm

WALTER L PALMER

IRRITABLE COLON

Definition—The most frequent cause of abdominal distress is disturbed intestinal motility primarily in the colon with more or less hyperirritability and hypersensitivity In various sections of the world different names are applied to the syndrome varying concepts are in vogue and multitudinous types of treatment are prescribed

None of the terms used to describe the functional bowel distress syndrome are entirely satisfactory Perhaps irritable colon" is the best for the bowel is irritable' as evidenced by the distress and by the abnormality of the stool Similarly descriptive are the terms unhappy and unstable colon Spastic or hypertonic constipation is usually only partially correct for the constipation" thought by the patient to be present is frequently absent Chronic functional colitis is a contradiction of terms for itis means inflammation and inflammation is scarcely functional' Cathartic colitis is perhaps applicable in cases with a cathartic habit Spastic colitis emphasizes the element of spasm rather than that of disordered function Mucous colitis is applied to those cases in which large amounts of mucus are expelled particularly the so called mucus

casts of the bowels The presence of such casts of dried mucus and cellular debris stained with fecal content does not basically differentiate this condition from the other types however because the secretion of mucus is a normal response of the bowel to irritation Less definite terms frequently used such as dyspepsia nervous indigestion gastric neurosis intestinal neurosis and so on do not all have identical connotations but fundamentally and practically the problems presented are the same and hence they may all be grouped together The condition is characterized by an abnormal irritability of the bowel with resultant abdominal distress and alteration in function The altered function consists of increased tone and motility with irregular and intermittent spasm

Etiology —In the absence of disease abnormal irritability may be related either to an excessive irritant such as laxative foods cathartics and enemas or to emotional disturbances or to a combination of the two The ability of castor oil and of fear to produce diarrhea are well established facts The chronic effects of laxative foods and of the emotional reactions to the difficulties of life are in certain individuals equally definite Symptomatically one sees all gradations from the chronic distress and diarrhea induced by the continued use of cathartics to the chronic complaints of the hypochondriac Usually it is difficult to differentiate sharply the physiologic and the psychologic or emotional factors and indeed as a rule it is unneces ary to do so Most important and never to be forgotten is the fact that distress of bowel origin and therefore technically bowel distress may accompany a variety of organic diseases Thus the cramps of bacillary dysentery or of intestinal obstruction are 'bowel but obviously not functional Physiologic toxic or reflex disturbances of the colon are seen in such diseases as pernicious anemia thyrotoxicosis pulmonary tuberculosis and pellagra These conditions are not included in the subject under discussion but the digestive symptoms may be confused

Symptoms —The symptoms of functional bowel distress vary in severity from fulness and discomfort induced by the ingestion of food or drink to severe cramplike abdominal pain This tends to be generalized over the abdomen may shift from point to point and usually is more noticeable in the lower than in the upper abdomen As a rule defecation or the expulsion of flatus affords temporary relief occasionally however the passage of a bowel movement inaugurates more vigorous cramps and tenesmus Nausea is a frequent symptom Many patients complain that they are unable to eat a full meal without experiencing an unpleasant sen a tion of fulness and distention perhaps sufficient to force them to discontinue the meal Belching rumbling and gurgling in the abdomen and excessive flatus are frequently noted Constipation is usually said to be present the patient meaning that it is neces ary to take laxatives or enemas in order to obtain a bowel movement When one inquires as to how long the patient goes without a defecation the typical response is 'I never let my bowels go more than a day without moving Thus patients say they are constipated whereas in fact they maintain a state of chronic diarrhea Many patients are obsessed with notions concerning the desirable frequency of defecation such as one after each meal or with ideas as to the optimal quantity assuring the physician dolefully that their bowels do not move enough Such patients are satisfied as a rule only by copious watery evacuations Inquiry into the type of stool passed usually discloses the fact that some abnormality is present such as loose watery stools unformed stools narrow ribbon like or lead pencil sized stools or hard dry balls The classic stools of lead colic are seen nowadays not in lead colic as a rule but in these functional disturbances The hard dry constipated stools when accompanied by abdominal distress are usually due to spasm—hypertonicity rather than atonicity Headaches fatigue and countless other nervous manifestations frequently present in such cases are not to be interpreted as due to alleged constipation or intestinal toxemia These symptoms as well as the bowel distress are usually on a functional" nervous or emotional basis It is surprising to note how frequently the therapeutic program outlined benefits them as well as the function of the digestive tract

Physical examination usually reveals a well nourished individual but occasionally

extreme grades of chronic malnutrition are noted The colon is often palpable and tender particularly the sigmoid portion Proctoscopy discloses a normal rectum and sigmoid The laboratory and roentgenologic findings are entirely normal Frequently the colon when examined with the barium enema exhibits evidence of hyperirritability, waves of mass peristalsis may be noted and the patient may complain of severe pain However, these changes are not sufficiently constant definite or regular in their appearance to justify reliance upon the roentgenologic diagnosis of an irritable colon

Diagnosis.—The diagnosis is based upon a history of catharsis or enema habit dietary indiscretion or emotional strain generalized or lower abdominal distress of the type described abnormality of the bowel movement and tenderness along the course of the colon

Differential diagnosis involves first the search for organic disease of the digestive tract *Carcinoma of the colon* particularly of the rectosigmoid should be excluded by examination of the stool for occult blood by x ray and by proctoscopy *Diverticulitis* may be detected by x ray although the mere demonstration of diverticulosis is not particularly significant *Ulcerative colitis* may be detected proctoscopically *Regional enteritis* may be suspected if the distress tends to be periumbilical or if there is roentgenologic evidence of a lesion of the small bowel *Carcinoma of the stomach* occasionally produces diarrhea and lower abdominal distress as does *carcinoma of the pancreas* The pain of *peptic ulcer* may be masked by bowel distress which may persist after the ulcer heals Cirrhosis of the *liver* passive congestion of the liver tuberculosis and carcinomatous *peritonitis* and other nondigestive diseases may be accompanied by these rather vague abdominal symptoms *Gallbladder disease* presents one of the most interesting diagnostic problems Acute bowel distress may simulate biliary colic On the other hand patients with cholelithiasis not infrequently have two types of distress (1) biliary colic and (2) so called biliary dyspepsia consisting of belching upper abdominal fulness and distention and aversion for fried or fatty foods The biliary colic is cured by cholecystectomy the dyspepsia frequently is not and may be relieved even without cholecystectomy by the program used in the management of bowel distress. The latter statement applies also to the alleged dyspepsia of so called noncalculous cholecystitis In fact it is doubtful whether gallbladder disease really produces dyspepsia at all The problem is similar to that which arises in connection with the appendix Acute and subacute and so called interval appendicitis produce the classic symptomatology of acute appendicitis Chronic appendicitis on the other hand may be found pathologically in a very high percentage of individuals with bowel distress just as it may be found in a high percentage of normal individuals Removal of the appendix or of a normal gallbladder or a diseased gallbladder is followed by good results in some cases and by bad results in others irrespective of the condition of the organ removed The major psychotherapeutic effect of an operation must always be borne in mind and care exercised in the drawing of *post hoc ergo propter hoc* conclusions The distress of these allegedly specific dyspepsias can usually be relieved by nonspecific measures A similar problem is presented by the gastritides found by the gastroscopists in approximately 40 per cent of all patients gastroscoped because of abdominal distress Except for certain erosive forms the relationship between the disease and the distress seems highly questionable Many of these patients present other manifestations of the irritable colon syndrome and respond very well to management Some physicians regard all patients included in the bowel distress group as psychoneurotics The great majority of them however pass for normal even as you and I some are frank psychoneurotics, others are hysterical a few are hopeless hypochondriacs some are more or less profoundly depressed some are psychotic

Treatment—Actually the first step in treatment is the relief of the patient s anxiety concerning organic disease Definite reassurance that there is no cancer or ulcer or some other serious condition cannot be given convincingly unless the examination has been detailed and careful Some patients however react with disappointment their thought being that they are ill that they

have pain and yet nothing has been found to be wrong It is then necessary to explain in detail the nature of the disorder, the cause of the pain and to outline the procedures for obtaining relief Superficial psychotherapy such as this is usually sufficient but frequently a deeper analysis of the patient and his problems is required In almost all cases in which the therapeutic program to be outlined is found ineffective the cause will be discovered to be either an unrecognized organic disease or a difficult often impossible psychiatric status

Laxatives and Enemas—The patient should be educated to obtain satisfactory bowel movements without the use of laxatives Hence cathartics of all kinds including mineral oil should be discontinued Diarrhea may ensue and may be controlled by regulation of the diet and by the drugs mentioned More frequently the patient will be surprised by the development of a normal bowel function Several days may elapse without defecation this is not alarming provided the rectum remains empty The only difficulty to be avoided is the development of a fecal impaction in the rectum Patients usually recognize the presence of such rectal masses but they may fail to do so Indeed not infrequently cramps and diarrhea result from the presence of a rectal impaction Consequently in the interval while waiting for the bowels to move digital rectal examinations should be made once or twice daily Ordinarily there is no danger in waiting several days even a week or two for feces to come down into the rectum but if a rectal impaction develops it should either be removed or broken up digitally following which a large tap water or soapsuds enema should be given repeatedly if necessary until the rectum is empty Oil retention enemas are of little if any value for this purpose but may be given prophylactically Three ounces of olive or mineral oil may be injected into the rectum at bedtime and retained over night if there has been no stool at all during the day or if the stool has been very hard and dry If no stool is passed by the following forenoon a small water enema (1 pint) may be given

Some individuals lose the normal defecatory reflex and are regularly unable to evacuate the stool—a so called *rectal dyschezia* Glycerin suppositories used at a regular hour are often helpful in re establishing the reflex Occasional patients solve this problem best by the daily use of a small enema half a pint or a pint of tap water Finally it should be pointed out that certain elderly people without abdominal distress should be permitted to continue their cathartic habit If they have no pain and have adopted a regime satisfactory to them there is no need to meddle with it

Rest and Exercise—In patients with a very irritable colon rest is of great value and conversely in patients with atonic constipation exercise is helpful The amount of rest indicated depends upon the severity of the disturbance When the pain is severe complete bed rest is in order In the average case long hours of sleep at night and perhaps a nap or rest period in the afternoon are adequate The application of heat to the abdomen in the form of hot stupes or more simply and conveniently an electric pad or a hot water bottle is advisable

Diet—The dietary management of bowel disturbance is based upon the varying laxative effects of different foods Anything which stimulates peristalsis may produce spasm and disordered function in a sensitive intestine Hence the diet must be adjusted to the sensitivity or irritability of the bowel All foods stimulate intestinal activity and thus are laxative There are no really constipating foods but there are marked quantitative differences in the effects of different ones There are also qualitative differences in their action just as there is a difference in the effect of magnesium sulfate and castor oil The irritative action of foods may be of a mechanical or chemical nature The classification on pages 716 and 717 is derived from tradition and experience

The average patient may be best handled by prescribing a diet estimated to produce the laxative effect required Thus temporarily he may be advised to select his diet from the first four sections only and be instructed specifically to eat a stipulated amount of cooked vegetable and cooked fruit perhaps two dishes of each daily a dish containing a liberal serving of approximately 100 Gm (3⅓ ounces) If diarrhea and abdominal distress continue on this

I *Foods with Little Irritant and Hence Best Tolerated in Acute Disturbances*

Water weak tea rice or barley gruel meat broth cream of wheat oven toasted toast, zwieback or toasted soda crackers with butter soft cooked eggs boiled milk custard plain jello

II *More Substantial but Relatively Bland and Easily Digestible Foods*

Cereals with milk or cream
- Refined rice
- Rice Krispies
- Rice Flakes
- Puffed Rice
- Cornflakes
- Puffed wheat
- Oatmeal (well cooked)
- Macaroni
- Noodles
- Spaghetti
- Vermicelli

Soups Consommé
- Strained chicken broth
- Strained vegetable soup
- Strained cream of rice soup
- Strained cream of potato soup
- Strained cream of celery soup
- Strained cream of mushroom soup
- Strained vegetable soup

Cheese Cream cheese
- American cheese
- Swiss cheese
- Cottage cheese
- Edam cheese

Fish Salmon
- Tuna
- Whitefish

Fowl Chicken
- Turkey
- Squab

Meats broiled boiled or roasted, or baked
- Beef
- Veal
- Lamb
- Ham
- Liver

Potato Baked mashed or au gratin

Breads White bread
- Toast
- Croutons
- Bread sticks
- Milk toast
- Hot biscuits of white flour
- Hot rolls
- Whole wheat bread

Milk products Milk, cream cocoa, eggnog butter

Other beverages Tea Sanka, Postum Coffee

Desserts Vanilla custard
- Caramel custard
- Floating island
- Rice custard
- Angel food cake
- Cream puffs
- Eclairs
- Icebox cake
- Ice cream plain
- Bread pudding
- Tapioca pudding
- Cornstarch pudding
- Spanish cream
- Plain cake
- Lady fingers
- Sponge cake
- Boston cream pie
- Pies Lemon cream
  - Banana cream
  - Coconut cream
- Bavarian cream
- Snow pudding
- Plain jello
- Cottage pudding
- Peter Pan cookies
- Hydrox cookies
- Arrowroot cookies
- Custard
- Chocolate

III *Cooked Vegetables—More Laxative Chiefly Because of Greater Residue*

A Moderately irritating
- Asparagus
- String beans
- Carrots
- Spinach
- Sweet potato
- Peas
- Tomatoes
- Beets

B More irritating
- Artichokes
- Parsnips
- Onions
- Cabbage
- Cauliflower
- Rutabaga
- Eggplant
- Green peppers
- Turnips
- Kohlrabi
- Broccoli
- Navy beans
- Lima beans
- Squash
- Corn

IV *Cooked Fruit More Laxative Because of Chemical Irritants*
- Prunes
- Peaches
- Applesauce
- Figs
- Apricots
- Pears
- Baked apple
- Plums
- Cherries
- Berries of all kinds
- Grapes
- Pineapple
- Rhubarb
- Fruit pies

V *Raw Vegetables More Laxative*
- Lettuce
- Celery
- Watercress
- Endive
- Tomatoes
- Radishes
- Onions
- Cabbage
- Cucumbers

VI *Raw Fruits More Laxative*

Banana (least laxative)	Pears
Oranges (juice sections whole)	Peaches
Grapefruit (juice sections whole)	Cherries
Apples	Grapes
Melon	Plums
Pineapple	Apricots
Berries of all kinds	Avocado pear

VII *Miscellaneous Foods Some Very Laxative Such as Honey and Beer*

Ice cream with fruit	Pickles olives relishes
Ice cream with nuts	Catsup
Jam, jelly marmalade honey	Soft drinks Coca Cola gingerale, sodas
Syrup	Alcoholic beverages beer wine, whiskey etc
Nuts	
Pop corn	
Candy	

schedule the fruit and vegetable content may be eliminated completely On the other hand it may be necessary to increase the intake of vegetable and fruit to three dishes daily specifically including liberal servings of spinach and prunes head lettuce and celery at least once per twenty four hours Usually it is not difficult to restore normal bowel function within a few days and to relieve the distress The diet should be continued for a few days or weeks before the patient gradually returns to a full menu Many individuals find it necessary to maintain some dietary restrictions permanently if they are to live comfortably Persistent pain and discomfort in the presence of normal bowel function is rarely of bowel origin There is no difficulty as a rule in selecting a diet adequate in caloric and vitamin requirements except in individuals with acute disturbances who are able to tolerate only a few of the foods outlined in section I Caloric deficiencies may usually be tolerated safely for the number of days required for the irritability to subside Vitamins may be administered hypodermically as desired although in the average case they are needed for a short time only

Drugs—The drugs of greatest value are the antispasmodics Tincture of belladonna is the standby given in doses of ten to fifteen drops three or four times daily Atropine is equally satisfactory 1/100 or 1/150 grain (0 0005–0 0004 Gm) three or four times daily In acute conditions 1/60 grain (0 001 Gm) may be given hypodermically Numerous atropine like preparations alleged to give superior effects on the bowel with fewer unpleasant side reactions such as dryness of the mouth and blurring of vision are of questionable superiority The barbiturates are very valuable and may be used in conjunction with belladonna 1/4 to 1/2 grain (0 015–0 03 Gm) of phenobarbital being given three or four times daily If insomnia is present the phenobarbital may be given to advantage at bedtime rather than throughout the day The drug exerts a desirable sedative effect not only on the general nervous system but also upon the bowel itself Bromides are equally satisfactory except for the hazard of bromoderma Opiates are as a rule to be avoided for they increase the tonicity of the gut Acute diarrheas are sometimes checked by opium or by morphine but the effect is accomplished by increasing the tone throughout the bowel and decreasing the peristaltic activity In chronic cases this effect in addition to the habit forming aspect is undesirable Codeine in doses of 1/2 to 1 grain (0 03–0 06 Gm) is much less objectionable and indeed at times is very helpful Paregoric although commonly used is not recommended for its active constituent is opium and few who use it know just how much opium it contains

WALTER L PALMER

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DILATATION OF THE COLON

It is sometimes hard to decide whether a colon is normal or dilated This difficulty arises from the fact that in normal individuals it varies enormously in size and hence differences of opinion naturally arise as to whether a given colon is dilated or merely normally large and tortuous The important consideration however, is not the size but rather the function of the colon Pathologic dilatations may be divided into (1) gaseous, (2) obstructive, and (3) megacolon or Hirschsprung's disease

Gaseous Distention —This is at times one manifestation of the functional bowel distress syndrome The more severe types occur as paralytic ileus following abdominal operations, as a complication of peritonitis, or of any febrile illness such as lobar pneumonia The distention of the abdomen pushes up the diaphragm, interferes with respiration and hence may present a serious complication

Treatment in the milder cases consists of the application of heat to the abdomen in the form of hot stupes or an electric pad and the limitation of oral intake to small amounts of warm nonirritating food such as barley gruel tea cream of wheat toast soft cooked egg Belladonna and phenobarbital are helpful because there is usually localized spasm as well as dilatation In the more severe grades nothing should be given by mouth A rectal tube may facilitate the escape of gas Enemas are frequently given usually of soapsuds or so called 1 2 3 enemas These frequently help the patient to expel considerable amounts of gas but at times they increase the pain and discomfort Morphine sulfate $\frac{1}{6}$ to $\frac{1}{4}$ grain (0 010 to 0 015 Gm) usually gives great relief and by increasing the tonicity of the gut helps the patient to expel gas Physostigmine in doses of $\frac{1}{30}$ grain (2 mg) subcutaneously and prostigmine 1 cc of a 1–2000 solution may be tried but are *not always effective* The inhalation of oxygen is often followed by dramatic improvement

The dilatation secondary to obstruction identified by locating the obstruction usually in the sigmoid or rectum ordinarily requires *surgical relief* although decompression of the *distended* loops of small intestine and colon by means of the Miller Abbott tube may be a life saving measure This procedure must be carried out however *with patience* and perseverance by someone who knows and understands the technique

Megacolon or Hirschsprung's Disease — *This is a congenital idiopathic* dilatation of extreme grade usually found in children In some cases the dilatation and hypertrophy *terminate at the rectosigmoid* in others they extend to the internal sphincter of the anus The child is usually stunted the abdomen is *relatively enormous, weeks or months* may elapse without a bowel movement As a rule the colon may be emptied by means of numerous *enemas and laxatives Some* patients continue to empty the bowel in this way taking a daily dose of senna by mouth and *supplementing its effect with two or* three enemas Various surgical procedures have been devised, the most radical being extirpa*tion of the colon and the most* satisfactory being section of the lumbar sympathetic nerves Spinal anesthesia alone temporarily *increases the activity of the colon* in such patients Neurectomy seems to be much more satisfactory in children than in adults

WALTER L PALMER

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DIVERTICULA OF THE INTESTINES

Meckel's diverticulum is the only significant diverticulum occurring in the jejunum or ileum It is a remnant of the omphalomesenteric duct which normally disappears within a few weeks after birth Not infrequently however it persists *more or* less completely as a fibrous tube *or cord*

arising usually from the ileum two or three feet from the ileocecal valve with or without a distal attachment to the umbilicus It may cause volvulus strangulation or intussusception

Acute inflammation of Meckel s diverticulum differs from acute appendicitis only in a more central periumbilical location of the pain—a differential point not too reliable Operation is indicated

Meckel s diverticula may contain islands of aberrant gastric mucosa secreting acid gastric juice Peptic ulcers developing in the mucosa of the ileum adjacent to the stoma of such diverticula are a common source of melena in infants and children and may occur in adults

Diverticulosis is a term used to denote the existence of diverticula The etiology is not known The incidence of diverticulosis in adults is approximately 5 per cent (Mayo Clinic) It is rare in children uncommon in young adults and occurs in increasing frequency with each advancing decade of life The descending colon and the sigmoid are involved most frequently and most extensively Diverticulosis is a silent benign condition frequently found in patients with bowel distress and apparently playing no role in the distress In *treatment* the diverticula may be disregarded

Diverticulitis occurs in only a small fraction of patients with diverticulosis It may be acute or chronic mild or severe Simple inflammation is likely to be associated with spasticity of the colon and hence simulates a spastic sigmoid When the inflammation is more acute signs of peritoneal irritation develop such as localized tenderness and muscle spasm Perforation may occur with localized peritonitis and abscess formation or generalized peritonitis Fistulae occasionally develop between the sigmoid and the urinary bladder as is indicated by the passage of urine containing gas or fecal material Obstruction may result from the intramural inflammation Ulceration of the mucosa is rare and hence rectal bleeding is usually due to hemorrhoids fissure of the anus or carcinoma The diagnosis is usually made by the history of recurring cramplike lower abdominal pains with tenderness and perhaps rigidity in the left lower quadrant and by the roentgenologic demonstration of diverticula with distortion of the pattern of the mucosal folds and an extensive ragged deformity of the contours of the bowel A mass in the sigmoid may be detected by abdominal palpation or by rectal examination Fever and leukocytosis may be present Neoplasm usually listed as a sequel of diverticulitis is probably merely a coincidence

The *treatment* of diverticulitis is rest in bed with heat (hot stupes electric pad or hot water bottle) applied to the abdomen The same dietary and medicinal principles may be applied as outlined in the section on functional disturbances of the colon Mineral oil may be given in doses of 1 or 2 ounces (30 to 60 cc) daily In rather rare cases the obstruction is sufficient to require either a permanent colostomy or resection of the most stenotic portion of the bowel

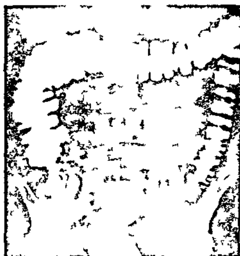


Fig 71—Chronic diverticulitis of the sigmoid. Patient J O (Unit No 237° 0) Male forty six years of age entered the hospital because of cramping lower abdominal pain of one week s duration The pain was sharp intermittent, relieved by the passage of flatus or feces A similar attack with leukocytosis seven years earlier had been treated by appendectomy but the *pain did not disappear until three weeks after the* operation A second attack four years later subsided spontaneously The stools in the present attack were described as watery Marked tenderness and moderate rigidity were present in the lower abdomen particularly on the left The temperature was normal and remained so the leukocyte count was 20 300 dropping to 11 000 on the third day The pain and tenderness subsided rapidly Note the coarse sawtooth appearance of the sigmoid

WALTER L PALMER

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NONSPECIFIC ULCERATIVE COLITIS

Nonspecific ulcerative colitis is an inflammatory disease of unknown etiology It may be limited to the rectum or involve the entire colon and even the terminal ileum The process is characterized initially by a friability of the mucosa with hyperemia and minute superficial bleeding ulcerations In fatal cases the entire colon is almost invariably involved and frequently there are one or more areas of disease in the small bowel The colon may be almost denuded of mucosa only occasional islands being left The areas of perforation found at autopsy may be so extensive as to suggest an autolytic process In less dramatic cases the longitudinal character of the ulcers suggests that pressure necrosis resulting from continued spasm may be a factor The degree of cellular reaction evident histologically in the wall of the bowel is quite variable often being surprisingly little and consisting chiefly of round and plasma cells with moderate numbers of leukocytes The disease seems to be increasing in frequency although as in so many conditions it is difficult to determine whether it is actually more prevalent or is merely recognized more frequently It occurs in both sexes and at all ages but particularly in the second third and fourth decades

Symptoms —The most benign type of the disease is that in which the inflammatory process is mild in severity and limited to the rectum or rectosigmoid In such cases the only symptom is the passage of red blood with each bowel movement The stools are usually well formed or even hard and dry Bloody mucus may be expelled without stool The presence of diarrhea usually indicates a more extensive involvement of the colon The number of stools may reach 15 to 20 per day or more with rectal incontinence There may be no pain at all and no abdominal tenderness in marked contrast to the spastic bowel In other cases cramps or tenesmus or both may be present and may be intense Fever occurs in the more severe cases leukocytosis is uncommon Loss of appetite is frequent, nausea and vomiting occur occasionally In the severe fulminating cases the onset is usually acute and the course rapid and severe with continued diarrhea inability to eat fever weakness anemia and profound debility Death may result from exhaustion or from perforation of the colon and generalized peritonitis The less severe cases may recover completely, more frequently they recover and then relapse occasionally they reach a stage of chronic invalidism with two or three somewhat bloody stools daily, roentgenologic and proctoscopic evidence of continued disease but without complete disability The more frequent complications are severe anemia perianal abscess perforation of the colon with local abscess formation or generalized peritonitis stricture formation polyposis of the bowel and rarely carcinomatous degeneration of the polyps

Theories of Causation —In general the theories concerning etiology may be divided into those relating to (1) infection and (2) emotion Pathologically and clinically the disease is indistinguishable from chronic bacillary dysentery except by positive bacteriologic evidence The well recognized difficulty encountered at times in isolating organisms of the dysentery group from cases of bacillary dysentery led early workers to look upon ulcerative colitis as chronic bacillary dysentery Apparently in the tropics there are numerous cases of chronic dysentery in which no pathogenic organisms are demonstrable A very attractive hypothesis suggests that the disease process is initiated by a specific dysentery and then maintained by ordinarily nonpathogenic organisms Felsen presented evidence that ulcerative colitis developed in a small percentage of people

afflicted with bacillary dysentery Occasional cases of amebic colitis are seen in which the colitis persists after the eradication of the amebae Numerous workers have found (a) that pathogenic organisms and parasites are present in only a small percentage of the cases of presumed nonspecific ulcerative colitis and (b) the serum of such patients does not contain in significant titer the antibodies of the known pathogens Endless search has been made for other possible etiologic organisms Hemolytic and nonhemolytic streptococci and staphylococci are frequently found diplococci and *B coli* are invariably present *Bacterium necrophorum* can usually be cultured if one uses the proper technic but none of those organisms has as yet been accepted as the causative agent or proved capable of producing the disease with any regularity in the experimental animal

The concept of a *psychogenic cause* is based on certain clinical and experimental evidence There is the well recognized capacity of fear to produce diarrhea Many patients afflicted with ulcerative colitis have very definite personality disorders Occasionally the relation between an emotional disturbance and an exacerbation of the disease seems too direct to be merely coincidence On the other hand the so called functional disorders of the colon almost never develop into ulcerative colitis and conversely the latter usually develops in individuals without previous digestive symptoms Experimentally Lium has produced ulceration of the intestinal mucosa as a result of spasm but the significance of this observation remains to be determined

Diagnosis—The diagnosis is established by a history of the symptoms described by the demonstration proctoscopically of a diffusely granular friable superficially ulcerated and bleeding mucosa and by the failure to find a specific cause for the inflammation The stool and also rectal swabs should be cultured for pathogenic organisms and a careful search made for *E histolytica* Usually if amebic colitis involves the rectum the ulcers are easily identified by their sharply punched out appearance the peripheral red halo and the areas of perfectly normal mucosa intervening between the ulcers but occasionally the picture is confusing The roentgenologic appearance is not pathognomonic Classically the colon loses its haustral markings decreases in caliber and in length and becomes somewhat fuzzy in outline

If the cecum and ascending colon are the portions of the bowel most extensively involved the possibility of tuberculous enteritis or amebiasis should be seriously entertained If the disease is limited to the rectum sigmoid and lower descending colon the roentgenologic appearance may be normal Conversely erroneous positive diagnoses may be made because the normal descending colon and sigmoid devoid of haustrations frequently present the straight tube like appearance considered typical of ulcerative colitis Lymphopathia venereum may produce a proctitis and sigmoiditis proctoscopically identical with the nonspecific form but usually stricture formation is present A history of buboes suggests and a strongly positive Frei test almost proves the diagnosis of lymphopathia venereum

Treatment—There is no specific therapy In the acute and subacute phases rest in bed is very important The application of heat to the abdomen in the form of an electric pad or a hot water bottle is helpful The diet should be as nonirritating yet as nutritious as possible (See Functional Bowel Disturbances) Meat is well tolerated The patient s weight and caloric intake should be watched constantly Accessory food factors should be given as indicated to compensate for the low intake and the possibility of poor absorption When bleeding is present a low prothrombin time is occasionally found indicating a need for vitamin K Belladonna may be used in large doses (40 to 120 drops per day) as tolerated Phenobarbital ½ grain (0 03 Gm) four times daily is valuable for its general sedative effect and for its effect upon the bowel Bismuth and chalk powders (bismuth subcarbonate calcium carbonate and calcium phosphate each 1.5 Gm) are usually not of much value but may be tried Opium may temporarily diminish the diarrhea but it is not recommended because it increases the tonicity of the bowel Occasionally however codeine in doses of ½ grain (0 03 Gm) when given with atropine or belladonna may be helpful Transfusions of whole blood or of plasma are of very great value Anemia is likely to appear early

and to become quite profound partially due to the inanition but more particularly to the continued loss of blood Consequently transfusions of whole blood are preferable they should be given in large amounts 500 cc to 600 cc at a time and as frequently as necessary to maintain a normal blood picture Various sulfonamides (neoprontosil sulfanilamide sulfadiazine sulfathiazole

fect the course of the disease Ileostomy m be indicated in the chronic cases not in fulminating ones for in these the patien chance of recovery is as great if not grea without surgical interference If after ile tomy active severe disease persists as e denced by recurring attacks of chills a fever or arthritis and bloody rectal d charge colectomy may be indicated Rare





Fig 72—Chronic ulcerative colitis Patient L G (Unit No 110985) a female twenty-one years of age entered the hospital in August because of bloody diarrhea and a 32 pound loss of weight The first symptom in January consisted of the passage of red blood in every stool In March appendectomy was performed for acute appendicitis Diarrhea appeared the day after the operation and persisted until admission averaging about ten watery bloody stools per day Lower abdominal cramps accompanied the diarrhea Twelve injections of emetin hydrochloride were given in June although *E histolytica* were not found Emaciation was evident, the abdomen was rather scaphoid and tender pitting edema was noted in both feet Red blood corpuscles, 2 9 million hemoglobin 52 per cent white blood corpuscles 14 100 Repeated stool examinations were negative for parasites and pathogenic bacteria but disclosed gross pus and blood During the first week of hospitalization the temperature ranged to 102 F then subsided During the subsequent eight months of hospitalization there were occasional febrile periods lasting one or two weeks the diarrhea gradually subsided the appetite and intake of food increased as did the weight The patient remained in bed at home for most of the time through the ensuing year the stools continuing to be well formed and without blood In the subsequent six years there have been occasional brief recurrences of blood in the stool with or without diarrhea Proctoscopic examination at such times has disclosed a granular friable mucosa with multiple small bleeding points at other times the mucosa of the rectum has appeared normal or slightly scarred The patient is working and seems in excellent health The roentgenogram on the left shows the shortened colon devoid of haustrations with an abnormal mucosal pattern throughout the transverse portion the picture on the right taken six and a half years later discloses a longer colon of normal caliber with a return of haustra in the transverse section

sulfaguanidine sulfasuccinyl and others have been tried extensively As is usually the case in any chronic relapsing disease 'good results have been reported It is clear however that few if any miracles have been wrought although some patients do seem to have been benefited The bacterial flora of the feces is altered markedly the normal coliform organisms being replaced by cocci and the total bacterial count greatly reduced These changes do not seem to af

is it feasible to restore the normal continuity of the bowel

Finally it should be emphasized that in few diseases is there required more patience and perseverance The treatment as in pulmonary tuberculosis must be continued for months and years most carefully and yet most tactfully In few conditions is there more need for the art of medicine

WALTER L PALMER

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REGIONAL ILEITIS

Definition —Regional ileitis is a nonspecific inflammation of the distal loops of the small intestine involving mainly the terminal segment and characterized by the formation of an ulcerating proliferating and cicatrizing granulomatous mass in this area Fistulous tracts from the ileum to the abdominal wall and from ileum to other adjoining hollow viscera commonly characterize the disease

Clinically the disease presents the picture of a low grade chronic infection of slowly progressive nature and ends by causing intestinal obstruction or lacking that by eventual inanition and exhaustion

Etiology —The disease is one of youth although its range throughout life is extensive The youngest case reported was eight years the oldest seventy one years of age The vast majority of cases fall into the decade between twenty and thirty years of life the average of a large series being twenty seven and one half years Ileitis is restricted to no geographic locality nor to any race or nationality It is now recognized through worldwide publications and case reports that the disease is probably universal in its distribution

No known single bacterial agent or virus can be held etiologically responsible for ileitis The disease is definitely not tuberculous since inoculations of laboratory animals with intestinal material repeatedly fail to demonstrate tuberculosis There may possibly be an association of ileitis with the dysentery bacillus some of the cases show fair serum agglutinations (1 80–1 160) and an occasional *Shigella dysenteriae* has been recovered from the stool The claim has also been made that ileitis like colitis has followed epidemics of intestinal dysentery Proof to date is lacking However multiple cases of ileitis in the same family have occurred five times in the last few years (brothers sister and brother two sisters and a niece etc) so that the suspicion of a common infectious agent seems justifiable

Morbid Anatomy —The granulomatous inflammation begins most often flush with the ileocecal valve and extends for 6 8 10 or 12 inches in an oral direction as a continuous cobblestone like ulceration accompanied by a dense thickening and infiltration of the submucosa muscularis and serosa Thence upward the areas of involvement may be interrupted to form skip areas separated by variable distances of apparently normal mucosa (12 18 or even 30 inches of uninvolved intestinal surface) Enlarged succulent mesenteric lymph nodes accompany the areas of intestinal involvement

The disease is not limited to the terminal ileum occasionally one sees the whole ileum or the ileum and the lower jejunum or the upper ileum and the whole jejunum involved a most unusual form is an involvement of a localized few inches isolated in some upper segment of ileum or jejunum the terminal ileum remaining free of disease

The cecum and the colon are rarely implicated only exceptionally does the process pass the ileocecal barrier to involve the cecum and ascending colon These are known as cases of combined ileitis and colitis or often as colo-ileitis

The slow perforation from a porous ul

cerated ileum may result in one of the most characteristic features of the disease namely, fistula formation These fistulas begin in the diseased ileum at the mesenteric attachment, they may end on the abdominal wall, particularly in the scar of a previous laparotomy or in any internal hollow viscus such as another intestinal loop a segment of colon or sigmoid the urinary bladder ureter, vagina or uterus

Quite commonly and very early in the course of the disease these fistulous tracts may appear as perirectal, rectal or rectovaginal fistulas preceding or accompanying the onset of active clinical manifestations of the disease

Symptoms —The commonest form of ileitis is the low grade chronic granulomatous type But acute ileitis does occur and is characterized by the sudden onset of severe cramps localized in the right lower quadrant, with fever ranging up to 102° to 103° F leukocytosis and mild usually unnoticed diarrhea The abdominal muscular rigidity tenderness and rebound tenderness simulate acute appendicitis and as such the case is usually operated upon as one of acute abdomen At the laparotomy the appendix is found to be normal the ileum beefy red and injected The mass is usually with good judgment returned to the celiac cavity resection is inadvisable and dangerous Such cases frequently subside and probably return to a normal status or they may progress to the more familiar and chronic form of ileitis

Chronic regional ileitis is characterized by a prolonged history covering several months or years of diarrhea abdominal pain loss of weight anemia fistula formation and eventually symptoms of intestinal obstruction The diarrhea consists of three to five or more mushy or semisolid stools containing mucus pus and occasionally gross blood The movements are accompanied by generalized abdominal cramps usually more marked in the lower quadrants Vomiting is unusual On abdominal examination a mass may frequently be felt in the right lower quadrant often in the region of the appendix or cecum but sometimes in the midline above the bladder or even in the sigmoid area The mass may be the size of a lemon or more often of a small orange tender and fixed Occasionally one may feel the gurgle of the passage of gas and fluid through the contracted intestinal lumen of the area under palpation

Approximately 10 per cent of cases of ileitis go on to eventual partial intestinal obstruction of a subacute severity Such obstruction is the end result of many years of ulceration and cicatrization and represents the attempt at healing and scar formation with encroachment upon the lumen of the intestine Obstruction is occasionally an initial symptom particularly in those cases in which the onset is acute and febrile In these instances the pathologic changes in the small intestine are usually extensive reach high up into the upper ileum and are based upon a diffuse inflammatory granulomatous change in the intestinal wall with considerable edema

The general condition of the patient suffers considerably but slowly as the disease progresses from year to year The loss of weight may be severe in older persons simulating carcinomatous cachexia anemia is moderate mild leukocytosis the rule particularly during the acute recurrences Minimal or occult blood in the stool is usual but gross hemorrhage from the bowel most exceptional

The course of chronic ileitis is a slowly progressive one spontaneous resolution rarely ensues Slow perforation in the right lower quadrant of the abdomen with localized peritonitis may occasionally end fatally More usually external fistulas or perirectal abscesses and fistulous tracts imperil nutrition and cause inanition and anemia

Diagnosis —The presence of an ileitis is based upon the finding of

1 A tender fixed mass in the lower abdomen

2 The presence of external fistulous tracts or perirectal abscesses or fistulas

3 Diarrhea milder than in colitis often intermittent

4 A low grade irregular fever

5 A negative sigmoidoscopy which should exclude the more common forms of ulcerative colitis

The clinical symptoms and the physical examination in a young person should suggest strongly the diagnosis which however should be confirmed by a thorough radio-

graphic study For this purpose a barium enema or preferably a barium meal should be instituted The barium enema should be continued until ileocecal regurgitation reveals the terminal ileum The barium meal should be followed hourly for three four five six, or seven hours until the terminal ileum is filled and visualized and photographed

In ileitis the terminal ileum presents the string sign of a distorted narrowed irregular lumen with the loss of mucosal pattern usually a six to nine hour delay in the distal ileum is observable Not every x ray is however confirmatory of the diagnosis at times the clinical impression is so positive that even in the absence of radiographic confirmation laparotomy is advisable

Ileitis is to be differentiated from sprue from primary ileocecal tuberculosis (an extremely rare disease) from diffuse Hodgkin s disease and disseminated lymphosarcomatosis of the small bowel Carcinoma of the ileum or jejunum is also much less common than ileitis and is difficult to differentiate In comparison with any of these diseases ileitis occurs with much greater frequency particularly in younger persons Its course is prolonged and indolent extending over years and rarely so severe or rapidly down hill as sarcoma Hodgkin s disease or carcinoma

Prognosis—The prognosis in ileitis is good as to life particularly in those patients in whom the process is limited to the terminal ileum and in which resections or short circuiting operations can successfully be performed In the complicated cases with fistulae to the external abdominal wall or to the internal viscera the prognosis while still good is altered by the complexity of the pathologic process The cases of diffuse ileo jejunitis offer in spite of extensive involvement a fairly good prognosis Diffusion of the process with its broad skip areas lessens the intensity of the disease at any one point The outlook under conservative medical care is comparatively good both as to life and as to healing of the inflammatory process

Treatment—No satisfactory medical treatment exists Supportive or expectant treatment in the form of a nonroughage diet vitamin replacement transfusions and sunshine help build up the general condition but the eventual therapy should be surgical

Chemotherapy—The use of some of the more recent sulfa drugs has been attempted in ileitis In general the results have been discouraging However in the cases of diffuse ileo jejunitis where surgery is obviously out of the question succinyl sulfathiazole (sulfasuxidine) is well worth a trial In several cases its use has led to apparent clinical betterment

Surgery—First choice is radical resection of the diseased terminal ileum cecum and ascending colon and the formation of an ileo transverse colostomy This is feasible and with comparatively low risk (approximately 10 per cent fatality) in most cases where the process is still a limited one and where too many fistulous tracts too extensive an intestinal involvement or a localized peritonitis has not yet occurred The resection must include all higher skip areas in the bowel lest recurrences appear at a later date

In cases where fistulous processes and infiltrating suppurative foci have occurred in the lower right pelvis primary resection is dangerous A short circuiting operation in such instances should generally be followed by a resection of the original process It is likely that the mesenteric lymph nodes represent the foci of residual infection and as in carcinoma these nodes serve as the point of origin of subsequent recurrences in the areas proximal to the surgical anastomoses For this reason wherever possible a primary resection with removal of all large succulent lymph nodes offers the very best chance for permanent cure

Where resection seems impossible or too dangerous an ileocolostomy with transection of the ileum is the second best choice The ileum must be cut across above the uppermost area of involvement so as to isolate and shut off the diseased area The ileocolostomy may be performed in the ascending or transverse colon or in the sigmoid

These short circuiting or palliative operations have a slightly lower mortality rate but are successful only in about 50 per cent of the cases When the symptoms continue in spite of such a conservative procedure a secondary resection of ileum and ascending colon is mandatory

Recurrences after resection are unfor

tunately too frequent (almost 15 per cent) and can be avoided only by making the original procedure so radical as to surely include in the excision all diseased areas

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APPENDICITIS

Definition —Appendicitis the most common major surgical disease is an inflammatory lesion of the vermiform appendix It may occur as an acute attack acute appendicitis which progresses to perforation or subsides spontaneously as mild recurrent attacks recurring appendicitis or if adhesions or obliteration follow infection a so called chronic appendicitis

History.—Laurence Heister[1] in 1711 found an abscess of the appendix at autopsy which he described in his Chirurgische Warnehmungen From the time that Mestivier[2] in 1759 demonstrated at autopsy an appendiceal abscess originating from a pin in the appendix the abscess having been surgically drained 141 cases of disease of this viscus were recorded in the literature before the paper of Reginald Fitz[3] in 1886 Fitz defined appendicitis and analyzed 257 cases of perforating ulcer of the appendix Kelly[4] states that To Thomas G Morton of Philadelphia, belongs the credit for the first successful removal of the appendix deliberately undertaken That was on April 27 1887 After this time the names of Ochsner Murphy McBurney and Deaver stand out as proponents of the surgical removal of the appendix and they did much to increase the knowledge of appendicitis and its treatment

Anatomy —In fetal life the appendix is a prolongation of the conical cecum As the cecum develops the lateral side grows more rapidly so that the appendix in the adult type of cecum comes off its medial wall about 2 cm below the entrance of the ileum The three longitudinal folds of the cecum converge at the appendix and are continued on it

The appendiceal mesentery arises from the under layer of the mesentery of the ileum and usually extends to the tip of the appendix It is however shorter than the appendix, a relationship which when exaggerated, accounts for unusual curving kinking or even spiraling of the appendix The appendiceal artery runs within the mesentery One of the most significant anatomical factors in disease of this viscus is that the appendiceal artery is a terminal vessel without anastomosis

The normal position of the cecum is in the right iliac fossa so here the base of the appendix is usually found (Figs 73 and 74) *The appendix itself may be found pointing* in any direction from this point (Fig 75) It may lie horizontally or may be directed into the pelvis or be directed upward behind the cecum—retrocecal appendix—or laterally The most frequent position is behind the ileocecal junction The retrocecal position is next most frequent In children the appendix is most frequently found directed into the pelvis

Etiology —Since the appendix is a blind tube the contents of which are discharged by peristalsis into the cecum mechanical factors may play a part in predisposing to infection The contents are of course heavily laden with bacteria particularly those of the colon group When the cecal outlet is blocked by fecal material stricture or a concretion a train of events is started which was described in the classic paper by Van Zwalenburg[5] in 1905 The efferent vessels which are within the resisting wall of the appendix *will be more or less occluded* by the greater pressure in the cavity Every atom of fluid which remains within the wall of the cavity adds its pressure to that already present and causes greater obstruction to the efferent current now if this occurred in perfectly sterile surroundings this balance might be maintained for some time without material harm enough fluid would filter through to maintain life in the cell But our cavity is far from sterile

With the circulation empeded the tissue cells deprived of their supply of food and oxygen offer little resistance to the attack of germs Wangensteen and his associates[6] many years later confirmed and extended these observations on the obstructive

mechanism in acute appendicitis To this etiological factor must be added the strepto coccal infections which are so frequent and which rise in frequency when acute res piratory infections are prevalent These two factors may act simultaneously

Symptoms —The classical symptomat ology of appendicitis is that of pain tender ness and rigidity in the right iliac fossa The symptoms vary according to the location of the appendix the extent of the disease and the individual reaction of the patient Nau sea and vomiting are usual but not con stant symptoms The temperature is usually

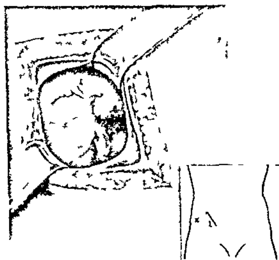


Fig 73 —Exposure afforded by the McBurney in cision Frequently no small bowel is seen except the terminal ileum

elevated but may remain normal for some hours following the onset of pain

Pain —In acute appendicitis pain is al most without exception the first symptom It most frequently comes on suddenly and is at first paroxysmal in character The first pain may develop around the umbilicus or in the epigastrium and later localize in the right iliac fossa but it must be emphasized that the later localization of the pain will depend upon the position of the appendix

Rarely acute appendicitis is present with little or no pain A history of nausea and tenderness upon pressure is however usu ally obtained When intense pain suddenly disappears perforation or gangrene of the appendix must be suspected This is the pe riod that DaCosta[7] called the calm before the storm Sometimes a constant dull pain

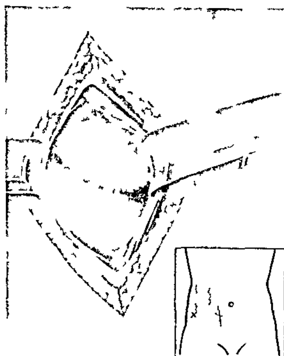


Fig 74 —Exposure afforded by a lower right rec tus incision Two loops of small bowel present in the wound. The author regards this as a definite disad vantage when a severely diseased appendix is to be removed because this area may be contaminated need lessly

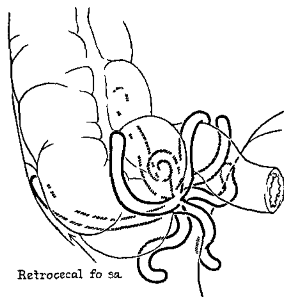


Fig 75 —Diagram showing some of the positions in which the appendix is frequently found

develops gradually in intensity This is rare in children but not uncommon in older pa tients

The first paroxysmal crampy pain may be due to distention of the appendix and is often associated with the presence of a fecalith The later, more constant pain is due to the involvement of the visceral and parietal peritoneum and is then dependent on the location and relations of the appendix As peritonitis extends the tenderness spreads with the process When an abscess develops the tenderness becomes localized Occasionally with an appendix which lies in the pelvis tenderness may be elicited only on rectal examination

When the disease is limited to the appendix tenderness may be slight but may be increased if pressure on the abdominal wall is suddenly released This sign rebound tenderness is a valuable aid in diagnosis when signs of the disease are not well defined

Rigidity—This reflex protection of the peritoneum which must be distinguished from voluntary rigidity varies according to the degree of pain and the extent of peritoneal involvement When present it is one of the most reliable signs of acute appendiceal disease although the degree of rigidity may vary widely in patients with a similar involvement of the appendix If the appendix lies low in the pelvis or if it is retrocecal the rigidity may be slight If the diseased appendix lies in contact with the peritoneum of the anterior abdominal wall the rigidity may be marked from the beginning With the spread of the infection to the peritoneum localized or even generalized board like rigidity may be present

Delicate palpation will elicit this sign much more accurately than deep pressure

Fever—There is nearly constantly some elevation of the temperature in acute appendicitis but this may be slight It is not uncommon to find the fever only 99° or 99 4° F but it may be as high as 103° F or higher This is true in the acutely obstructed appendices with infection and following perforation The fever is more apt to be low than high Chills are rare in uncomplicated appendicitis but are relatively frequent when the vascular supply to the appendix becomes involved

Leukocytosis—Leukocytosis of some degree is to be expected This varies greatly but as a rule a count of over 20 000 cells per cu mm raises a question as to the diagnosis or strongly suggests perforation Ten thousand or over should be considered as suggestive in the presence of other symptoms and signs of appendicitis In children the leukocyte count is frequently higher than in the adult Polymorphonuclear leukocytosis may be present with a practically normal total white cell count

Nausea and vomiting are frequently present but may be entirely absent In children vomiting may be the first evidence of appendicitis

Differential Diagnosis—The differential diagnosis is influenced by age and sex

In the child fever and abdominal pain may be due to a *gastro intestinal disturbance* in which colic is present but localized rigidity and tenderness are usually absent

Pneumonia with referred pain from diaphragmatic irritation may simulate appendicitis and presents one of the most difficult problems in differential diagnosis Rapid respiration and absence of rebound tenderness aid in the diagnosis but the most valuable sign is absence of tenderness or a mass on rectal examination *Lymphadenitis* of the mesenteric glands presents a real problem in diagnosis especially in the first attack A more gradual onset a low leukocyte count and more general tenderness lead one to suspect this condition but accurate differential diagnosis is often difficult and at times impossible

After puberty in the female a *ruptured graafian follicle* may be impossible to differentiate from appendicitis If the hemorrhage is extensive there may be faintness A normal temperature a high leukocyte count and the occurrence of the pain at the mid period of the menstrual cycle are suggestive However this diagnosis is usually made after the abdomen is opened *Torsion of an ovarian cyst* is also a diagnosis that is difficult to make before operation unless the cyst is large enough to be felt on rectal or vaginal examination

A ruptured tubal pregnancy may as a rule be diagnosed from the history of missed menstruation by the signs of intra abdominal hemorrhage by localized tenderness on vaginal examination and a history of some vaginal bleeding Since this is also a surgical lesion the diagnosis is of importance mainly

because of the selection of the type of incision to be used

Acute salpingitis with right sided pain may be differentiated by the history of burning on voiding and a vaginal examination which will show a cervical discharge and localized tenderness in the pelvis The sedimentation rate is greatly increased The signs will usually be more pronounced than the general illness of the patient In infection of a pelvic appendix giving as many signs and symptoms the patient is usually acutely ill

Acute cholecystitis may offer a problem for a high lying appendix and a low lying gallbladder may give tenderness in nearly the same region In acute cholecystitis however the tenderness will be located along the lower border of the liver and often the gallbladder can be felt The reference of pain in gallbladder disease is usually to the back and right shoulder If the patient is not seen before there are signs of abscess formation the surgeon must make the decision as to the optimal time for operation and whether the appendix should be removed at the time the abscess is drained

Diverticulitis of the colon usually occurs on the left side and the onset of symptoms is more gradual However a *ruptured diverticulum* of the ascending or even descending colon and a ruptured appendix may have identical symptoms

Ureteral stone and *infection of the right kidney* may give symptoms referred to the right lower quadrant but the tenderness in kidney infection will be felt when the kidney is palpated and the urine will as a rule contain blood or pus The initial pain begins as a rule in the back and radiates to the suprapubic area However an acutely inflamed appendix lying over the ureter may give rise to all of the symptoms so that it seems better to operate for rarely does the patient in whom the diagnosis is incorrect die following operation but if one waits until peritonitis more accurately leads to the diagnosis the mortality must remain high

Treatment —The treatment of acute appendicitis is surgical removal of the appendix as early in the disease as possible If the patient is not seen before there are signs of abscess formation the surgeon must make the decision as to the optimal time for operation and whether the appendix should be removed at the time the abscess is drained There is no medical treatment for acute inflammation of this viscus It is of course of first importance that if appendicitis is suspected nothing be given by mouth until the diagnosis is certain Laxatives should never be given if there is any possibility of appendiceal involvement because of the danger of perforation

Prognosis —The prognosis depends upon the extent of the infection at the time of operation and it is for this reason that prompt diagnosis is of such importance When the infection is limited to the appendix there should be practically no mortality from this operation The mortality is proportional to the extent of the spreading infection and it must be remembered that perforation is not necessary for the presence of peritonitis The rapid spread of peritoneal infection usually indicates perforation near the base of the appendix Careful postoperative treatment has done more to reduce the mortality in appendicitis with peritonitis than any change in operative technic In acute suppurative appendicitis the use of sulfonamides locally and parenterally has reduced the mortality in a number of clinics by more than 50 per cent Sulfonamide therapy does not take the place of sound surgical principles in the care of these patients

Chronic Appendicitis —This is a term which has in recent years been used less and less frequently since the process to which it should refer is not a continuous low grade infection but recurrent attacks of infection with residual scarring and adhesions Vague constant or burning pain in the right iliac fossa will seldom if ever be relieved by appendectomy If a patient has a history of repeated attacks of pain in the right lower quadrant with fever and nausea and vomiting during the attacks the diagnosis of recurrent appendicitis must be considered and if other causes for the pain can be eliminated the appendix should be removed during the attack or in the interval between attacks The appendix in these cases may be found firmly bound down by adhesions or attached to other viscera such as the ileum fallopian tube or ovary the ureter or even to the under surface of the liver

Appendicitis in Children—The cardinal symptoms of appendicitis are similar in the child and adult but are more difficult to elicit in the child because of lack of intelligent cooperation The signs also may be obscure in a crying infant Frequently in a child the first symptom that is noticed is vomiting and refusal of food Since a young child may have such symptoms from dietary indiscretions all too frequently the parents have given a cathartic before consulting a physician A careful examination will elicit the signs of rigidity and tenderness the tenderness frequently being found only on rectal examination The fundamental difference in the progression of the disease in infants and children is due to the late development of the omentum In the child the short omentum cannot as effectively wall-off a perforation and confine the infection to the ileocecal region as can the fully developed adult omentum The pelvic appendix is less easily walled off and here too the child is at a disadvantage

The etiology of appendicitis in children is the same as in adults but with the addition of occasional cases due to the oxyuris

Acute infection of the mesenteric lymph glands is especially frequent in childhood Slight or even moderate fever and pain may be present The differential diagnosis is important but the absence of localized tenderness and the more generalized pain in lymphadenitis often aid in making this It is better to operate on a case of lymphadenitis than to fail to operate on a case of acute appendicitis Under the age of two while the disease is relatively uncommon the mortality is very much higher than in the adult

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INTESTINAL OBSTRUCTION

Definition—Intestinal obstruction or ileus may be defined as a diminution absence or reversal of the normal flow of the intestinal contents due to partial or complete occlusion or to inadequate propulsion Whereas in common usage the term usually signifies an actual mechanical hindrance to progression of intestinal contents it should be realized that this is a restricted conception and that the condition may also be produced by disturbances of intestinal motility resulting from nervous or vascular influences

Etiology—Undoubtedly the largest number of cases of intestinal obstruction are caused by mechanical agents which actually interfere with forward motion of the intestinal contents This may be produced by various factors which can act by actually plugging the lumen constricting the tube or compressing it from the outside Accordingly the various factors which may produce mechanical obstruction can be classified into three types (1) intraluminal (2) mural and (3) extramural Examples of the first type which has been referred to as obturation are foreign bodies gallstones bezoars enteroliths and worms The mural type is typified by hernia volvulus and compressive tumors Ileus may also be produced by certain functional nervous disturbances resulting in peristaltic failure Ileus may be classified into two types (1) adynamic (inhibitive or paralytic) ileus and (2) dynamic (spastic) ileus Failure of peristalsis may also be produced by vascular insufficiency in which the musculature of the bowel loses its capacity for contractile response This is exemplified by mesenteric thrombosis and embolism The following classification of intestinal obstruction is based upon these conceptions

Etiology

I Mechanical Obstruction
- A Intraluminal
  - Obturation
    - Foreign bodies gallstones enteroliths worms inspissated feces and barium
- B Mural
  - 1 Congenital atresia
  - 2 Imperforate anus
  - 3 Strictures
  - 4 Adhesions
  - 5 Intussusception
  - 6 Neoplasms
- C Extramural
  - 1 Hernia
  - 2 Volvulus
  - 3 Compression

II Functional Obstruction
- A Adynamic (inhibitive or paralytic) ileus
- B Dynamic (spastic) ileus

III Vascular Obstruction
- A Mesenteric thrombosis
- B Embolus and infarction
- C Hemorrhage

It should be realized that although intestinal obstruction may be produced independently by any one of these three principal mechanisms *i e* mechanical functional or vascular it is possible and not infrequent that one becomes superimposed upon the other and that they even act concurrently Moreover the initial operation of one factor may not be sufficient to produce complete obstruction but the additional effect of one or both of the other factors is enough to eventuate occlusion Thus the original cause of obstruction may be an adynamic ileus following operation If adequately treated early this may be of no consequence but if the distention is allowed to progress a segment of bowel may become twisted and produce actual mechanical occlusion of the lumen or the distention may be sufficiently extensive to produce circulatory embarrassment in the wall of the involved lumen Similarly in hernia the lumen of the involved segment may be only partially occluded but sufficiently to hinder the propulsion of the intestinal contents The resultant stasis and dilation cause interference with venous return thus increasing the edema of the bowel wall this further augments the constriction resulting in complete occlusion and even strangulation Hence partial mechanical occlusion becomes converted into complete obstruction by the addition of the vascular factor

Special Types of Obstruction —*Obturation Ileus* —Obturation ileus may be defined as that form of ileus in which a mechanical obstruction is caused by intraluminal agents These may be of different types such as gallstones intestinal parasites fecaliths enteroliths concretions bezoars food boli miscellaneous foreign bodies meconium and epithelial casts This type is rare comprising about 2 per cent or less of all types of ileus

In addition to normal feces which under abnormal conditions such as Hirschsprung s disease may become inspissated and impacted the accumulation of excessive amounts of vegetable material resulting from ingestion of various indigestible substances such as celery fibers skin stems and seeds can produce obstruction Also the imbibition by painters or furniture workers of furniture polish because of its high alcoholic content may result in the deposition of concretions consisting principally of shellac

In the case of gallstone ileus the stone is usually quite large and gains entrance into the gastro-intestinal tract by passing directly from the fundus of the gallbladder into the duodenum by erosion and the production of a cholecystoduodenal fistula In most instances of obturation ileus the obstruction occurs in the distal ileum because this is the narrowest part of the small bowel In obturation ileus there is a great likelihood of erosion occurring because of the pressure necrosis which is produced by the hard foreign body

Congenital Atresia —By congenital atresia is meant an absence of the lumen due to some failure or arrest in the normal embryologic development of the intestinal tract The condition appears about once in every 20 000 births The condition is frequently associated with other congenital anomalies such as heart disease cystic kidneys and malformations of the extremities The lower ileum is the most frequent site of involvement Multiple areas are present in about 15 per cent of cases The degree of involvement varies from stenosis or narrowing of the lumen to complete occlusion

Imperforate Anus —Imperforate anus and atresia of the lower portion of the rectum occur about once in 5000 births with equal

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Imperforate Anus—Imperforate anus and atresia of the lower portion of the rectum occur about once in 5000 births with equal

sex incidence The condition may be explained on the basis of arrests or abnormalities of embryologic development of the post-allantoic gut Failure of closure of the cloacal duct results in fistulous communication between the rectum and genito urinary apparatus Accordingly, two types of imperforation are observed (1) simple imperforation, and (2) those imperforations associated with fistulous communications which are usually rectoperineal or in the male rectovesical and recto urethral and in the female rectovaginal The character of the obstruction varies from stenosis to atresia with the rectum terminating as a blind sac for variable distances above the perineum

Strictures —Intestinal obstruction may be produced by strictures which narrow or occlude the lumen These strictures may be congenital or acquired benign or malignant The acquired cicatricial forms may follow mechanical or operative trauma vascular injury such as infarction or bacterial or inflammatory reactions As a cause of intestinal obstruction they are relatively rare

Any form of bowel ulceration with subsequent cicatricial healing may result in sufficient narrowing of the lumen to produce obstruction Of these regional enteritis which is frequently multiple, is one of the most common Other forms of ulcerative processes are those associated with tuberculosis bacillary dysentery ulcerative colitis and typhoid fever Diverticulitis especially of the sigmoid and occurring usually in older patients may produce sufficient inflammatory reaction to cause obstruction Rectal strictures are most commonly produced by granulomatous processes such as syphilis and lymphogranuloma inguinale

Trauma incident to intra abdominal operative procedures and faulty anastomoses may cause stricture formation Accidental trauma also may give rise to the condition by vascular injury of the mesenteric vessels and production of hematoma or infarction Traumatic stricture may also follow reduction of strangulated hernia especially the femoral type Irradiation therapy for pelvic malignancies has been known to produce obstruction by stricture formation

The pathologic features are those of mechanical obstruction and the type of lesion producing the occlusion Regional enteritis strictures are frequently multiple and most commonly involve the lower ileum and cecum In ulcerative colitis and amebic lesions the strictures involve varying lengths of the colon In granulomatous lesions which most frequently concern the rectum the degree of involvement may vary from ring-like constriction to contraction of the entire rectum In practically all forms the degree of obstruction may vary from simple narrowing to almost complete occlusion The obstruction is almost invariably of the simple type and strangulation rarely complicates the condition

Adhesions Ileus —Adhesions are responsible for approximately a third of all cases of intestinal obstruction and the majority of these follow intra abdominal operative procedures or infections Of the operations appendectomy is the most frequent and gynecologic procedures are next Drainage of the peritoneum is believed to increase the liability The pathogenesis of these adhesions is not thoroughly understood Fibrinous peritoneal adhesions normally occur as a localizing protective mechanism to various forms of mechanical clinical or bacterial trauma Once this process has served its usefulness the fibrinous adhesions are normally digested by proteolytic ferments In some cases, however they become organized and replaced by fibrous adhesions In addition to postoperative adhesions ileus may be produced by congenital bands and adhesions such as the avascular fold between the terminal ileum and cecum adhesions which follow endometrial transplants tuberculous peritonitis and other non-operative peritoneal infections The mechanism of adhesions ileus varies but is usually due to kinking traction torsion or actual compression The presence of Meckel s diverticulum may initiate an obstruction by these various processes

Intussusception —Intussusception may be defined as the invagination of one portion of the intestine (the intussusceptum) into usually an adjacent, more distal segment (the intussuscipiens) This is the descending type the ascending or retrograde type is rarely observed Intussusception comprises about 5 per cent of all cases of intestinal obstruction and is the most common cause in children Approximately 75 per cent of

the cases occur in children less than two years of age and 50 per cent in those less than one year The ratio of males to females is about two to one Various causative factors have been cited but in infants in whom the condition is most common there is usually no apparent cause According to some observers the pathogenesis may be explained on the basis of irritation of the mucous membrane by varying agents particularly strong cathartics structural peculiarities which permit excessive mobility dysfunction of nervous control or incoordination and the presence of excessive lymphoid tissue about the ileocecal valve and terminal ileum Other etiologic factors particularly in adults include the presence of Meckel s diverticulum pedunculated tumors carcinoma inflammatory lesions and foreign bodies

FOUR TYPES of intussusception have been recognized (1) *enteric*—entirely within the small intestine (2) *ileocecal*—the ileocecal valve forming the apex of the invaginated bowel (3) *ileocolic*—invagination primarily of the ileum through the ileocecal valve and (4) *colic*—entirely within the colon The ileocecal and the ileocolic types are the most common Whereas usually there is no actual occlusion of the lumen in intussusception the obstruction is due to the active contraction of the sheath particularly at the neck In addition to this because of the tension of the mesentery of the intussusceptum and its compression vascular disturbances are liable to occur early Accordingly the greatest pathologic changes are found in the intussusceptum which soon becomes edematous indurated and engorged with blood There is excessive mucous secretion extravasation of blood into the lumen and eventually especially in the irreducible form ulceration gangrene and perforation

Neoplasms—Exclusive of hernias as a cause of intestinal obstruction neoplasms comprise about one sixth of the cases and are among the most frequent causes in patients past middle life These include benign and malignant tumors the former arising most frequently in the small bowel and the latter in the colon Lipoma fibroma adenoma and angioma comprise the benign tumors The malignant tumors include primary and metastatic carcinoma and sarcoma Primary carcinoma is by far the most frequent type of lesion and most commonly involves the colon *Carcinoid tumors* frequently referred to as argentaffinomas usually occur in the appendix and lower ileum and give rise to obstruction Whereas carcinoma situated in any part of the large bowel may produce obstruction it is more liable to occur in the left half and approximately half of the cases are in the sigmoid Metastatic carcinoma may produce intestinal obstruction by contiguous growth usually from primary lesions arising in the pelvic adnexa by distant implantation and involvement of neighboring loops or by lymphatic extension and eventual encirclement of the bowel Occasionally in both benign and malignant tumors the obstruction is precipitated by the development of intussusception especially in the presence of polypoid growths Volvulus may also occur Inflammatory swelling and edema are particularly important factors in precipitating acute obstruction in carcinoma of the large bowel

The pathologic features are those of mechanical obstruction and of the type of neoplasm concerned In cases in which chronic obstruction has preceded the acute attack there may be hypertrophy and edema of the bowel wall above the site of obstruction Because of the mechanism of the ileocecal valve in preventing regurgitation colonic obstructions are converted into closed loops with consequent circulatory embarrassment or strangulation Accordingly gangrene and perforation are more liable to occur in these forms Perforation may also be due to the malignant process

Hernia—External hernias are by far the most frequent cause of intestinal obstruction comprising almost 50 per cent of the cases A much smaller number is caused by internal hernias Inguinal hernias are the most frequent cau e of intestinal obstruction and of the hernial obstructions the next most frequent are femoral umbilical and incisional Hernias are of importance in the production of ileus not only because of the mechanical obstruction offered by the presence of an intestinal loop in the hernia and compression at the neck but also because of the liability of early vascular interference consequent to compression of the vessels in the mesentery In addition to compression of

the intestinal loop at the hernial orifice, an increased accumulation of gas and fluid in the imprisoned loop tends to produce an intramural strangulation In some instances the herniated loop of bowel may become adherent to the hernial sac and hence irreducible This is less likely to be associated with an acute obstruction than is the case in which the hernial orifice is relatively small and in which the loop is readily reduced

The distention of the herniated loop of bowel is caused by the accumulation of gas and fluid forced into the isolated loop by the propulsive power of the intestine and to the relative inability of the herniated loop to evacuate them through the compressed distal loop It is for this reason that rigid hernial rings are more liable to produce intestinal obstruction and strangulation than those in which the orifice is more pliable Intestinal obstruction associated with external hernias are more readily recognized than those associated with internal hernias because of their obvious presence In cases where there is vascular interference (strangulation) varying degrees of color change are observed in the bowel from cyanosis to the greenish black discoloration of actual gangrene

Volvulus —By volvulus is meant torsion or twisting of a segment of bowel on its mesenteric axis usually in a clockwise direction Volvulus comprises about 10 per cent of all cases of intestinal obstruction It is usually due to increased length or defective fixation of the mesentery permitting abnormal mobility of the attached loop of bowel Coarse vegetable diets on an empty gastro intestinal tract violent catharsis or other stimulation of overactive peristalsis unusual physical exertion or other traumas such as falls or jumps have been considered as precipitating factors The ileocecal area and sigmoid are the most frequent sites of involvement the former being more common in children and the latter in adults Its incidence is slightly greater in males As a result of the torsion and consequent compression of the mesenteric vessels especially the veins circulatory disturbances occur early Venous engorgement develops first and hemorrhagic infarction finally occurs The involved segment of bowel becomes edematous discolored and eventually gangrenous and perforated The distended loop due to extravasation usually contains more fluid than gas There may be evidence of localized peritonitis and free peritoneal fluid

Functional Obstruction —Functional obstruction may be defined as failure of normal propulsive peristalsis resulting from a disturbance in the nervous mechanism or contractile response This type of intestinal obstruction may be classified into two forms (1) adynamic (inhibition paralytic) ileus, and (2) dynamic (spastic) ileus

A mild form of ADYNAMIC ILEUS occurs following almost all intra abdominal operations and is probably due to splanchnic irritation This moderate degree of intestinal paresis is manifested by slight distention and inability to expel gas and the subsequent gas pains indicate the return of peristaltic activity Whereas adynamic ileus is observed most frequently following peritonitis and other intra abdominal lesions such as strangulation of the omentum, renal and biliary colic torsion of an ovarian cyst, retroperitoneal hematoma and infections it may also occur following extra abdominal lesions and systemic infections It has been observed following fractured ribs or other bones spine injuries and blunt trauma to the abdomen Pneumonia typhoid fever meningitis and other infectious diseases may be associated with severe adynamic ileus Embolism and thrombosis of the mesenteric vessels also produce this type of obstruction and it may be superimposed upon or follow mechanical ileus In these conditions there is the additional factor of circulatory embarrassment which by interference with the blood supply of the intestinal musculature further reduces its capacity for contractile response The common conception that in this condition the intestinal wall is paralyzed is erroneous for it has been repeatedly demonstrated experimentally and clinically that following interruption of sympathetic impulses by splanchnic block or spinal analgesia the ability of the intestinal musculature to contract is normal Most observers believe that the condition is due to hyperactive sympathetic influence Accordingly the term "reflex inhibition ileus is more accurately descriptive than paralytic ileus The dilatation which may vary in degree from mod

erate to extreme usually involves the entire intestine and the bowel wall appears thin and dusky Clinically the condition is characterized by pronounced meteorism due mostly to swallowed air and in contradistinction to mechanical obstruction colicky pain is absent Moderate tenderness may be present and auscultation reveals a relatively silent abdomen In contradistinction to the mechanical forms of ileus these patients characteristically appear euphoric and exhibit less anxiety

DYNAMIC OR SPASTIC ILEUS is rare and in contrast to adynamic ileus is characterized by actual spastic contraction of a segment *of the bowel usually the colon Various* causative factors have been observed including lead poisoning injuries irritating intraluminal contents or mural lesions such as foreign bodies intestinal worms ulcers tuberculous peritonitis neurasthenia and hysteria renal colic and infectious fevers Cases have also been observed in which there is a combination of dynamic and adynamic ileus The condition is believed to be due to disturbances arising in the intrinsic nervous mechanism of the bowel wall The pathologic features consist of constriction and thickening of a segment of bowel with occasional ring like contractions The bowel above the collapsed segment is dilated with an accumulation of fluid and gas Gangrene and perforation do not occur Clinically the condition closely simulates mechanical obstruction and neurotic tendencies frequently may be detected

Vascular Obstruction—Vascular obstruction usually results from interference with the blood supply to a segment of bowel This is most commonly caused by occlusion of the mesenteric vessels Arterial occlusion due to thrombosis and embolism is slightly more frequent than venous and affects the superior mesenteric artery more frequently than the inferior Venous thrombosis is usually due to infection especially of the portal radicals Other initiating agents are strangulation trauma and prolonged alcoholic bouts The pathologic features consist essentially of edema distention discoloration with transudation of serosanguineous fluid into the lumen and the peritoneal cavity gangrene and eventual perforation of the infarcted segment The usual clinical manifestations consist of sudden acute abdominal pain, shock vomiting diarrhea and melena

Pathologicophysiologic Changes in Ileus—In acute intestinal obstruction especially if the obstructing lesion is located high in the intestine there occur certain characteristic biochemical changes consisting essentially of dehydration hypochloremia alkalosis hemoconcentration increased nonprotein nitrogen and urea and possibly hypopotassemia Most of these at least the dehydration dechlorination alkalosis and hemoconcentration can be explained on the basis of loss of fluid and electrolytes from the upper intestinal tract Normally the *upper portions of the alimentary tract* are secretory and the lower are absorptive It has been estimated that about 7000 cc of fluids consisting of gastric secretions succus entericus bile and pancreatic juice are poured into the gastric and upper intestinal tract daily and under normal conditions most of this is absorbed in the lower portions of the intestine If there is an interference with the normal transportation of these large quantities of fluid stagnation and dilatation occur in the upper intestinal tract with consequent nausea and vomiting and loss of these fluids The loss of these fluids and electrolytes (the sodium and chloride ions) is largely responsible for dehydration The alkalosis may be explained on the basis of the loss of the acid radical chloride Normally the sum of the basic ions in the plasma must equal that of the acid ions sodium comprises the greater part of the former and chloride the latter The body s attempt to maintain this equivalence in the presence of relative deficiencies of one or the other of these ions is based upon the adjustability of the bicarbonate ion In the gastric juice there is a greater amount of chloride ion and in the bile and pancreatic juice a larger quantity of sodium ion In high intestinal obstruction there is a greater loss of chloride ion (because the vomitus contains a greater amount of gastric juice [and hydrochloric acid]) than sodium ion and the relative excess of the basic ions principally sodium is compensated by an increase in bicarbonate ion with resultant alkalosis The hemoconcentration which is observed particularly in high intestinal obstruction may be due in part to the dehydration fol

lowing the loss of fluids but also in part to the loss of plasma into the lumen and the wall of the involved intestine

In addition to the above biochemical changes practically all cases of ileus show a gradual accumulation of gas and fluid proximal to the obstruction which produces distention of the bowel The gas in the dilated loops of bowel is to a large extent (about 70 per cent) due to swallowed air

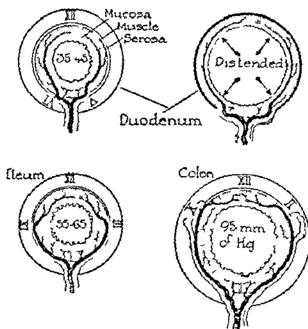


Fig 76—Diagrammatic illustration of relative position of intramural vessels and resultant effects of increased intra-enteric pressure in various parts of intestinal tract If cross section of bowel is represented by the face of a clock with mesenteric attachment at six o clock the vasa rectae pierce the muscularis in the case of the duodenum at approximately five and seven o clock in the jejunum and ileum at nine and three o clock, and the colon at two and ten o clock Thus in the duodenum any increase in intra intestinal pressure results in considerable compression of the relatively long vessels which lie between the mucosa and the muscularis whereas in the colon because the greater portion of the vessels lies outside the muscularis an increase in the intra intestinal pressure exerts little effect on the blood supply

Another possible source of the increased amount of gas is that derived from putrefaction of food and disturbances in gaseous interchange A large portion of the gas in a distended loop of bowel is nitrogen possibly due to the fact that it is less readily absorbed than other gases Similarly the fluid accumulation is an important factor in producing dilatation This is partly due to the failure of propulsion of intestinal fluids from the secretory portion of the gastro-intestinal tract into the lower absorptive areas

The *symptoms* and *prognosis* in acute ileus are largely dependent upon the viability of the bowel wall In those cases in which there is an interference with the blood supply to the intestine the patient is much sicker appears much more toxic and is more liable to die early than is the patient without strangulation Also everything else being equal the higher the obstruction the worse the prognosis and the more rapidly progressive the course Whereas many are of the opinion that in high intestinal obstruction the progressive deterioration of the patient is due to the excessive loss of fluids and electrolytes there are others who believe that in these instances the early interference with the blood supply by compression of the vessels within the wall of the intestine that is an intramural strangulation is the responsible factor Interference with the blood supply may occur either in the mesenteric vessels or within the wall of the gut as a result of increased intra-enteric pressure. That the upper part of the intestinal tract is particularly vulnerable to distention has been shown repeatedly Dragstedt Lang and Millet have shown that there is considerable variation in the intramural blood vessels in different parts of the intestine and that as a result of this anatomic fact pressure within the gut exerts varying influences on the blood supply of the intestine (Fig 76) In instances in which there is an interference with the blood supply whether it be mesenteric or intramural there is transudation of fluid into the lumen and through the wall with transperitoneal absorption of bacteria and other lethal agents Obviously as the intra enteric pressure increases interference with the venous return from the bowel wall increases thus augmenting the capillary hydrostatic pressure and resultant filtration pressure The associated anoxia produces increased capillary permeability and all these factors result in considerable loss of plasma and aggravation of the ileus If distention is permitted to continue long enough and there is sufficient intramural compression actual necrosis of the gut may occur particularly on the antimesenteric surface where perforation is most liable to be found

Symptoms—The symptoms of intestinal obstruction vary and depend upon the degree and site of occlusion In general sudden acute mechanical occlusions located high in the intestinal tract produce more intense and earlier symptoms than other forms Similarly in strangulation the manifestations are more severe than in simple obstruction Whereas such variations exist with the type and extent of obstruction the cardinal manifestations irrespective of the cause are essentially pain vomiting distention and constipation

Pain is usually the first symptom especially in acute mechanical obstruction It is characteristically intermittent and colicky occurring in severe paroxysms with crescendo rises and after being sustained at a maximum intensity for several minutes it ceases abruptly Early the pain may be located at the site of obstruction but is frequently referred to the mid abdomen Between the paroxysms there is little discomfort except in the presence of strangulation These paroxysms are usually more intense and frequent in small than in large bowel obstruction As distention progresses and the contractile response decreases the intensity and paroxysmal character of the pain recede Whereas paroxysms of colicky pain are characteristic of mechanical obstruction there is little or no pain in functional ileus

Vomiting also varies in intensity and character depending upon the type and site of obstruction In general the higher the obstruction the earlier and more severe is the vomiting At first the vomiting is reflex and although this may occur in other acute abdominal conditions the type of vomitus is particularly significant in intestinal obstruction After the stomach has been emptied of a previous meal by reflex vomiting retching may be unproductive or the vomitus may consist only of bile stained gastric juice This is soon followed by the regurgitation of a grayish glairy material characteristic of intestinal contents especially in high obstruction If the obstruction is low however the appearance of this material may be delayed for hours Although at first this material has a faint odor of moldy food later it develops a fecal or stercoraceous odor which is not necessarily an indication of colonic contents for the fecal odor may be due to protein putrefaction occurring in the small bowel Colonic obstruction even when pronounced is frequently associated with little or no vomiting except the initial reflex vomiting This may be explained on the basis of the ileocecal check valve mechanism which is usually competent and permits fluids and gas to enter the colon but prevents their regurgitation

Constipation is an eventual occurrence in all cases of ileus but may not be significant early Immediately after the onset of an acute obstruction there may be one or two spontaneous bowel movements due to emptying of the intestinal tract distal to the obstruction In fact a history of defecation occurring at the same time as or shortly after the onset of pain with no subsequent bowel movements is frequent in acute intestinal obstruction In incomplete obstruction small diarrheic movements also may occur The presence of blood in the stools indicates strangulation blood and mucus intussusception

Chronic intestinal obstruction may be due to many of the conditions which produce the acute type It is most commonly caused by slow growing benign or malignant neoplasms of the bowel which progressively encroach on the lumen inflammatory and granulomatous lesions of the bowel and intrinsic defects in neuromuscular mechanism such as Hirschsprung s disease Characteristically the onset is insidious and the principal manifestation is constipation which becomes progressively worse Resort to laxatives and purgatives which produce temporary relief is frequent but becomes increasingly necessary and progressively less effective Recurrent attacks of abdominal discomfort colicky pain and distention are common In aged individuals fecal impaction is not infrequent The presence of hemorrhoids and blood streaked stools may also be observed

Physical Findings—Although the signs of acute intestinal obstruction are quite typical there is some variation with the stage and site of obstruction At onset the general appearance of the patient reveals no significant changes As the disease progresses towards a more advanced stage and dehydration and other physiologic disturbances have occurred the characteristic anxious expression with pinched facies fast

thready pulse and cold clammy extremities becomes evident In strangulation and in the late stages of other forms of obstruction in which there is vascular insufficiency of the *involved bowel shock may develop* as the result of blood loss

Abdominal *distention which is due to dila*tation of the bowel proximal to the obstruction is also an eventual occurrence in all cases of ileus It is more likely to be pronounced in lower ileal and colonic obstructions but in early, particularly in high obstructions is characteristically absent Although distention eventually becomes generalized with barrel like abdomen it may *be localized at first Thus* in high obstruction the distention may be limited to the upper *abdomen, while in low colonic* obstruction a prominent fulness appears on each side of the abdomen and extends across the abdomen along the course of the large bowel In advanced stages of lower ileal obstruction a characteristic ladder pattern on the abdominal wall representing dilated intestinal loops may be apparent

Visible peristalsis, which usually indicates *hypertrophy of the bowel is more char*acteristic of chronic obstruction but may be present in acute ileus especially in patients with a thin abdominal wall Furthermore abdominal tenderness and rigidity are not prominent features of simple acute obstruction Although there may be some tightening of the abdominal muscles during paroxysmal attacks of pain the abdomen is re*laxed between these attacks Tenderness and* rigidity indicate peritoneal irritation and their presence suggests strangulation and peritonitis consequent to leakage or perforation

Because of its early and constant character, auscultatory evidence of hyperperistalsis is particularly *significant The loud* whirring gurgling sounds can frequently be *heard* readily without a stethoscope However, auscultation with a stethoscope over various parts of the abdomen may be helpful not only in diagnosing an acute ileus but also in locating the obstruction Characteristically in intestinal *obstruction* these sounds (borborygmi) are heard with greatest intensity at the height of the paroxysmal attacks of pain With progress of the ileus the whirring sounds change to tinkling notes In the late stages of obstruction and in adynamic ileus the abdomen is silent

Laboratory Findings—The characteristic alterations in the blood and urine are probably the result of dehydration and loss of chlorides and electrolytes Hemoconcen*tration is usually* present with increased values for hemoglobin, erythrocytes and leukocytes The *blood chlorides* are decreased and the carbon dioxide combining power and nonprotein nitrogen are increased The urine is scanty and albumin and indican may be demonstrable Whereas these findings are characteristic of acute high obstruction, they usually do not appear until about forty eight hours after the onset and may be readily corrected by the administration *of saline solution and other fluids*

Roentgenographic examination is undoubtedly one of the most valuable diagnostic procedures in acute intestinal obstruction A scout film taken with the patient in the prone position will aid in localizing the site of obstruction by revealing gas in the small intestine only in *obstructions of* the small bowel and in the colon with rela*tively little in the small intestine* in obstructions of the large bowel Because the fluid in the various dilated loops of bowel will assume a level with the gas above a skiagram taken with the patient in the upright position will reveal numerous fluid *levels* Contrast substances should not be given by mouth in cases of suspected *intestinal* obstruction but in obstructions of the colon a *barium enema* may be helpful in determining the site of occlusion In gallstone ileus roentgenography is of value not only because the calculus is sometimes opaque and can be visualized but also because the roentgenographic visualization *of gas* in the biliary tract resulting from the cholecystenteric *fistula is pathognomonic*

Prognosis—The prognosis in intestinal obstruction depends upon a number of factors among the most important of which are the type and extent of obstruction integrity of the blood supply and the *time* elapsing between the onset and the institution of therapy *Thus the mortality* in obstructions due to external hernia is *comparatively low* in spite of frequently associated strangulation because the diagnosis can *be made* relatively early and rational therapy *ie*

operation is usually not delayed On the other hand, the mortality in obstructions due to mesenteric thrombosis and embolism is relatively high because the diagnosis is less obvious and necrosis perforation peritonitis and shock are likely to develop earlier

According to reported statistics the total mortality varies from 17 per cent to over 60 per cent In spite of recent intensive clinical and experimental investigations the general mortality is still inexplicably high Three main theories have been advanced to explain the high fatality rate The first and oldest is based upon the concept that a potent toxin is formed in the obstructed intestine and is produced by specific or non specific bacterial growth putrefaction or abnormal mucosal changes or secretions The second theory is based upon the hypothesis that death is due to loss of fluids and electrolytes The third concept that death is related to the element of shock was suggested by the 'shock like manifestations of patients with late acute intestinal obstruction It should be realized that none of the theories is wholly acceptable and that they have been controversial subjects among investigators for many years More recently attention has been directed to the significance of the distention factor and the importance of increased intra enteric pressure in diminishing mesenteric venous absorption

Treatment —Whereas the treatment of acute intestinal obstruction may vary according to the type and degree of obstruction in general the two principal therapeutic objectives consist essentially first in the correction of local and systemic disturbances produced by the obstruction and second removal of the obstructive agent and restoration of normal bowel function

The systemic disturbances which may be pronounced especially in high obstruction consist essentially of dehydration hypochloremia and hemoconcentration These can be combatted by the administration of *saline solution* and *other fluids* as soon as the diagnosis is established Although the loss of electrolytes is a more important factor in high obstruction dehydration plays a significant role in all obstructions The required amount of fluids and saline must therefore be determined in the individual case and will depend upon the site degree and period of obstruction Salt may be administered best in the form of physiologic saline solution and periodic plasma chloride determinations will aid in gauging the salt requirements Determinations of specific gravity of the plasma and the hemoglobin will also indicate the degree of hemoconcentration or dehydration Fluids can be administered in the form of 5 per cent dextrose solution After the initial dehydration and hypochloremia have been combatted adequate hydration can be maintained by the simple method of determining urinary excretion In the presence of normal kidney function sufficient fluids should be administered to permit daily urinary excretion of about 1200 cc

Because the patient often cannot take food by mouth for a number of days *maintenance* of *caloric* and *nitrogen equilibrium* becomes important Accordingly intravenous feedings are necessary The use of 10 per cent or even 20 per cent solution of dextrose administered slowly as an intravenous drip over long periods will aid greatly in meeting the caloric requirements Nitrogen equilibrium may also be sustained by the intravenous administration of amino acids and plasma transfusions Whole blood and especially plasma transfusions are particularly important in cases of vascular obstructions such as mesenteric thrombosis or embolism and in acute mechanical obstructions such as volvulus intussusception and hernias accompanied by strangulation In such cases sufficient blood and plasma loss in the involved segment of bowel may produce serious blood volume reductions eventuating in shock like manifestations Obviously this may be readily combatted by the restoration of normal circulating blood volume with whole blood and plasma transfusions The increasing significance of vitamin requirements has been recently demonstrated In these cases the most important vitamins are B and C which may also be administered intravenously

The significance of distention has been emphasized and is undoubtedly one of the most important of the local factors requiring therapy This may be realized by the fact that in spite of combatting all of the systemic factors mentioned above and the

maintenance of fluid and salt balance, life cannot be sustained long if acute distention of the small intestine remains unrelieved *The significance of decompression* therefore becomes increasingly evident Decompression may be achieved by means of intubation or enterostomy Decompression by intestinal intubation is best accomplished by the use of a double tube or double lumen tube (Miller Abbott) with an inflatable rubber balloon a few inches proximal to a perforated metal tip The tube is inserted through the nose and down the esophagus into the stomach and once the tip is well past the pylorus so that the balloon lies in the duodenum this is inflated and continuous suction applied The inflated balloon stimulates peristalsis by pressure against the intestinal wall and acts as an object of sufficient bulk to permit propulsion downwards Thus as the tube progresses continuous suction removes the accumulated fluid and gas in successive loops of distended bowel and permits decompression and consequent resumption of normal peristalsis which in *turn draws the tube farther downward* This process is continued until the site of obstruction is reached In cases of adynamic (inhibitive) ileus the procedure is also applicable and the mechanism of decompression is similar Whereas this method of decompression is of inestimable value in cases of simple acute mechanical obstruction it should not be attempted in strangulating obstructions or those limited to the colon by a competent ileocecal valve Such cases require early operative intervention Enterostomy which prior to the development of intestinal intubation was commonly employed as a decompressive procedure is now rarely used although it is occasionally justified in certain localized forms of mechanical obstruction

Of great value in the treatment of ileus is the administration of *morphine* or other opium alkaloids Contrary to general conceptions morphine exerts a powerful tonic effect on gut musculature and is helpful in combatting *intestinal distention and its consequent* intramural strangulation both in mechanical and adynamic ileus Extensive investigations have demonstrated that other drugs are of little or no value in ileus

The *inhalation* of a high concentration of *oxygen* has also been found a valuable adjunct in the treatment of intestinal obstruction This is based on the experimental demonstration that the intraluminal pressure produced by gas, especially nitrogen may be appreciably diminished by the inhalation of pure oxygen A possible explanation for this observation is based upon the greater *diffusibility of oxygen and its consequent* replacement of the nitrogen An additional value of this therapeutic procedure lies in the beneficial effect of better and more effective oxygenation in those patients whose respirations are impeded by the pronounced distention and whose respiratory function is diminished by the use of morphine

The second therapeutic objective *ie removal* of the *obstructing agent* and *restoration* of *normal bouel function* must be achieved for complete recovery In the majority of cases surgical intervention is necessary although in some cases of simple mechanical obstruction due to adhesions hernia volvulus or intussusception and also in certain cases of inhibitive ileus the conservative management with decompression and other supportive measures referred to above is sufficient to restore intestinal continuity Conservative decompression should not be prolonged unduly however and if there is no appreciable improvement *in* from twenty four to thirty six hours *operation* should not be delayed Immediate surgical intervention is necessary in strangulating obstructions and acute colonic *occlusions* wi pronounced distention However even i such instances operation should not be at tempted in the presence of considerable de hydration shock or other complications (obstruction which *would* jeopardize th chance of recovery For *this* reason it is de sirable in all cases to improve the patient general condition before operation by uppe gastro intestinal decompression hydration transfusion and other supportive *measures*

Once the decision of surgical interventio has been made the type of procedure indi cated will depend upon the condition foun at *operation* This *in turn is* greatly in fluenced by the viability of the bowel *Thus* in mechanical obstruction due to adhesion or hernia in which after release of the ob struction the bowel is found to be viable Or simple closure *is all that* is necessary

the other hand if the bowel is no longer viable excision of the involved segment with subsequent anastomosis is necessary This may be done by primary resection or by exteriorization of the necrosed portion In some cases especially in the presence of malignant tumors an initial short circuiting procedure or entero anastomosis with subsequent resection may be preferable In certain cases of simple obstruction exploration and removal of the obstructing agent are undesirable and the procedure of choice is the simplest and the least traumatic Under these circumstances an enterostomy or colostomy should be done above the site of occlusion

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INTESTINAL NEOPLASMS

Incidence —The intestine is one of the most frequent sites of primary neoplasms about 15 per cent of all cancers arise in the intestines Whereas there is some variation in the relative incidence of different types of tumors in various parts of the gastro intestinal tract in general it may be stated that slightly more than one-half occur in the stomach about two fifths in the colon and rectum and less than one-tenth in the small intestine Of all tumors in the gastro intestinal tract about four fifths are malignant and one fifth benign However this ratio varies in different parts of the alimentary canal Thus although in the stomach about nine-tenths of the tumors are malignant in the colon and rectum about three-fourths are malignant and in the small intestine only slightly more than two-fifths are malignant About 45 per cent of all benign tumors and 37 per cent of all malignant tumors in the gastro intestinal tract are located in the large bowel whereas only about one-fourth of all benign tumors and less than 5 per cent of all malignant tumors are located in the small intestine Of all intestinal (small and large bowel) neoplasms slightly more than four fifths are located in the large bowel and of the malignant tumors almost nine-tenths are in the large bowel

The etiology is unknown but stasis chronic irritation infection embryonic tissue rests and morbid changes in Brunner s glands have been suggested as possible factors The relative infrequency of cancer of the small bowel as compared to other parts of the intestinal tract is significant but no satisfactory explanation has been presented

Small Intestine —*Benign Tumors* —In the small intestine benign tumors are rela

tively more common than malignant neoplasms and tend to occur at younger ages than the latter There is no significant sex incidence Included among the benign tumors are adenoma, lipoma fibroma, myoma hemangioma chylangioma, accessory pancreatic tissue, enterogenous cysts and gas cysts Of these *adenoma* is by far the most common and occurs most frequently in the ileum and next in the duodenum Usually single, they may be multiple and polypoid They vary in size from a few millimeters to several centimeters in diameter Grossly they resemble other polyps and histologically they are characterized by benign hypertrophy and hyperplasia of glandular epithelium of the mucous membrane The potential danger of malignant change in benign adenomatous intestinal polyps should be remembered *Lipomas* are believed to arise from the areolar tissue in the submucosa or subserosa are usually single tend to be pedunculated and are rarely more than a few centimeters in diameter Pure *fibromas* are relatively rare They may be sessile, pedunculated and project into the lumen or externally The tumor appears as a discrete freely movable rather firm mass which microscopically shows connective tissue *Myomas* grossly resemble other benign tumors but histologically are characterized by strands of smooth muscle fibers Hyaline degeneration and hemorrhagic necrosis are common *Hemangioma* and *chylangioma* are extremely rare in the small bowel Chylangiomas are softer more cystic and gray or yellow in color Accessory *pancreatic tissue* or aberrant pancreatic rests are believed to originate as misplaced pancreatic tissue and accordingly are found most frequently in the duodenum and upper jejunum They appear as small irregular rather flattened submucous nodules closely resembling normal pancreatic tissue *Enterogenous cysts* are extremely rare and are believed to arise as a result of some anomaly of embryonic development

The CLINICAL MANIFESTATIONS of benign tumors of the small intestine are variable and depend upon location type and character of the tumor Many never produce symptoms and are recognized accidentally at laparotomy or autopsy Symptoms are usually due to erosion or ulceration and consequent hemorrhage or to intestinal obstruction produced by intussusception or by gradual encroachment on the lumen Tumors in the duodenum usually produce manifestations of progressive obstruction Epigastric pain nausea, vomiting and distention are prominent symptoms Hematemesis and melena are not infrequent As the obstruction increases vomiting and distention become more pronounced Abdominal tenderness is usually present but rigidity is seldom elicited

The DIAGNOSIS is based upon these clinical manifestations and the roentgenologic demonstration of duodenal obstruction or a filling defect representing the tumor In the jejunum and ileum the clinical manifestations are also usually those of obstruction caused by intussusception or gradual occlusion Approximately a fourth of the cases of benign tumors in this segment of the bowel cause obstruction by intussusception and in adults intussusception is most frequently caused by tumors in the ileum In the other forms obstruction is produced by gradual encroachment on the lumen and the symptoms are more insidious The PHYSICAL FINDINGS vary with the stage of the process at first there are few signs except possibly some tenderness and if the tumor is of sufficient size a palpable mass Roentgenologic examination especially with the aid of a double lumen tube passed down to the site of obstruction is of distinct value in the diagnosis

The PROGNOSIS in uncomplicated benign tumors of the small intestine is relatively good Complications such as hemorrhage perforation intussusception, and complete intestinal obstruction increase the gravity of the condition

TREATMENT consists of early and complete surgical extirpation In some cases this necessitates intestinal resection

Malignant Tumors.—Malignant tumors of the small intestine include carcinomas sarcomas and carcinoids or argentaffin tumors Of these carcinoma is probably the most common with sarcoma next in frequency

Carcinoma of the small intestine occurs more frequently in the male sex with the highest incidence in the fourth fifth and sixth decades The duodenum especially the second or periampullary portion is the re-

gion of greatest involvement Several forms of carcinoma of the small intestine are recognized depending upon their gross pathologic or histogenic characteristics Grossly, the most common is the ring type which produces constriction or stenosis Next is the infiltrating ulcerative type which is pearly and firm and has a fibrous appearance The third type is the polypoid form which appears as a fungating mass protruding into the lumen Many believe that these arise as a result of malignant change in a pre-existing benign adenomatous intestinal polyp Histologically these carcinomas are classified into four types adenocarcinoma medullary scirrhous and colloid

The CLINICAL MANIFESTATIONS are variable and depend upon the location size and character of the tumor and the degree of malignancy They are predominantly those of intestinal obstruction A history of abdominal distress and pain is frequent Pain is usually colicky in character and accompanied by nausea and vomiting As the degree of obstruction progresses these attacks increase in frequency and severity Loss of weight and strength and even cachexia are characteristic of malignant growths Tumors of the duodenum may produce hematemesis and melena or symptoms of duodenal ulcer Those located in the periampullary region may produce biliary obstruction and the consequent painless jaundice develops early Malignant tumors of the jejunum and ileum produce symptoms usually of greater intensity but similar to those described for benign tumors in this area with obstruction as the predominant feature When the tumor becomes sufficiently large a movable palpable mass may be present Roentgenography is of diagnostic value especially with the aid of a double lumen tube which can be passed to the site of obstruction

The PROGNOSIS in primary carcinoma of the small intestine is not good Metastasis occurs early and extends first to the regional lymph nodes and peritoneum and then to the liver lungs and other organs

TREATMENT consists of radical resection when the tumor is removable In the non resectable tumors because of extensive metastasis palliative operations for relief of obstruction may be necessary

Sarcoma of the small intestine is about twice as frequent as sarcoma of the large bowel and occurs most commonly in males and in middle aged individuals Depending upon their histogenesis the various forms of sarcomas of the small intestine include lymphosarcoma leiomyosarcoma fibrosarcoma and neurofibrosarcoma Lymphosarcomas comprise two thirds of the cases and leiomyosarcomas about one fourth These tumors especially lymphosarcoma occur most frequently in the ileum and next in the jejunum Lymphosarcoma is believed to originate in a simple lymphoid follicle or in lymphoid tissue located in the submucosa and in the early stage is localized in this region as a soft friable mass It grows by spreading along the tissue spaces and soon infiltrates the muscularis and other tissue layers of the bowel wall This tendency to invasion and destruction of surrounding structures is shown by the cylindrical or rigid tube-like character of the tumor growth Ulceration is late and when it occurs it is characteristically excavated Obstruction may occur as a result of stenosis, intraluminal protrusion or external compression of the tumor intussusception or kinking or by adherence of coils of intestine Metastasis occurs to the regional lymph nodes in the mesentery and especially to the liver Melanosarcoma or malignant melanoma of the small intestine is rare and usually occurs in the rectum It is usually multiple and appears as a polypoid or bosselated tumor with a bluish to black color

Sarcomas of the small intestine produce CLINICAL MANIFESTATIONS which vary from those of acute intestinal obstruction to symptoms of vague abdominal disorders More commonly there is colicky abdominal pain accompanied by nausea and vomiting some fever gradual loss in weight and secondary anemia Occasionally the onset is sudden with manifestations of acute obstruction perforation and severe hemorrhage. Diagnosis is difficult and is based upon the history of colicky abdominal pain loss of weight and strength the presence of secondary anemia and an inconstantly palpable tumor Roentgenologic examination of the small bowel is of value especially with the aid of a double lumen tube which may be passed to the point of obstruction

PROGNOSIS is poor as metastasis is fre-

quent Treatment consists of radical extirpation when this is possible Radiation therapy, especially for the lymphoid type is of some value

Carcinoid tumors, also known as argentaffin tumors because of their affinity for silver dyes are believed to arise from what is known as the chromo argentaffin cells of the normal intestinal mucosa most numerously located in the appendix and terminal ileum and believed in some way related to the chromaffin system These tumors occur most commonly in the ileocecal region with the appendix and especially its tip as the most frequent site Grossly they appear as small rather freely movable nodules varying in size from 0 5 to 1 cm in diameter with a firm somewhat rubbery consistency and a characteristically bright yellow color Lying beneath the mucous membrane they tend to obliterate the lumen of the appendix or bowel Histologically they are characterized by nests or columns of cells surrounded by a stroma of connective tissue and smooth muscle The cells which are fairly regular contain distinctive nuclei and a granular cytoplasm with an affinity for silver They are usually single and commonly regarded as benign but should be considered potentially malignant because about a fifth of the cases show malignant characteristics with considerable enlargement of the original tumor and metastasis to the liver and regional nodes

These tumors appear in either sex and at any age but most commonly in young adults Their CLINICAL FEATURES depend to a great extent upon their location In the appendix the manifestations simulate chronic appendicitis In the small intestine they are symptomless unless they become of sufficient size to obliterate the lumen and then the manifestations are those of intestinal obstruction In the stomach colon and rectum they produce symptoms resembling malignancy The PROGNOSIS is relatively good especially if recognized before metastasis has become widespread Recurrence is rare TREATMENT consists essentially of surgical excision

Colon and Rectum —*Benign tumors* of the colon include epithelial papilloma or adenoma lipoma fibroma myoma myxoma adenomyoma and enterogenous and gas cysts Of these adenoma and lipoma are probably the most common

Adenomas are polypoid tumors which may be sessile or pedunculated single or multiple and limited to one segment of the bowel, or diffuse producing generalized polyposis of the colon The condition appears more commonly in males and in middle or late adult life although the diffuse type which is rarer is encountered more frequently in younger persons Chronic inflammatory lesions of the bowel are believed to be of etiologic significance in the development of these neoplasms According to Erdman and Morris two types of adenomas of the colon may be recognized those known as the adolescent or congenital type which are disseminated and those referred to as the adult or acquired type The former appear as sessile or pedunculated soft round masses of variable size projecting into the lumen and are uniformly distributed in the colon or rectum The latter type is similar in gross appearance but more frequently limited to one segment of the bowel especially the rectosigmoid Histologically they consist of hypertrophic glands on a stalk of connective tissue with a rich vascular supply Whereas both types may undergo malignant change the adult type is more liable to be affected in this manner The potentially malignant character of these adenomatous polyps should be emphasized and many observers believe that all carcinomas of the large bowel arise from polyps

Other benign tumors such as *fibromas lipomas myomas* and *angiomas* may also be polypoid in character They may be sessile or pedunculated single or multiple and are usually symptomless unless they encroach on the lumen or cause intussusception and obstructive symptoms Hemorrhage may be caused by cavernous hemangioma Adenomyoma is due to the implantation of endometrial tissue on the serosal surface of the bowel or the appendices epiploicae As a result of deeper extension into the bowel wall constriction of the intestine may occur

The CLINICAL MANIFESTATIONS of benign tumors of the colon vary with the type of growth and the presence or absence of such complications as hemorrhage intussusception or other obstructive features Solitary pedunculated tumors may produce inter

mittent attacks of localized colicky pain They are a frequent cause of intussusception especially in the adult Adenomatous polypi especially the multiple forms produce more characteristic symptoms There is usually a history of repeated attacks of gastro intestinal upsets with cramp like pain diarrhea hemorrhage from the bowel and the passage of mucus In the diffuse forms the attacks are frequently associated with profuse hemorrhage and secondary anemia However even in the adult type moderate hemorrhage is common Alternating attacks of diarrhea and constipation are not uncommon Progressive loss of weight and anemia are indications of malignant change In cases in which the tumor causes obstruction the symptoms will depend upon the nature and degree of constriction

The DIAGNOSIS of benign tumors of the large bowel is made on the basis of the clinical manifestations and the roentgenologic and proctoscopic findings Solitary tumors that project into the lumen may be demonstrated by roentgenographic studies following the introduction of a radiopaque material Multiple polyposis can usually be demonstrated either by this means or by proctoscopic visualization

The TREATMENT is essentially surgical and consists of excision In cases of obstruction preliminary enterostomy may be necessary Because of their potentially malignant nature polypi should be treated by radical resection of the involved bowel (colectomy) The solitary type with a long pedicle may be excised at the base Polyps limited to the rectum may be treated by fulguration through the proctoscope

Malignant tumors of the large bowel are among the most frequent tumors of the body It is stated (Rankin and Graham) that carcinomas of the colon comprise 15 per cent of all carcinomas In addition to carcinomas other malignant tumors are sarcomas of which lymphosarcoma is by far the most frequent Sarcomas however occur most infrequently In the consideration of tumors of the large bowel it is desirable to differentiate between the proximal and distal halves of the colon because they have different origins different functions and different types of lesions The proximal half of the colon up to the mid portion of the transverse colon is derived from the mid gut and is therefore closely allied to the small bowel The distal portion of the colon that beyond the mid portion of the transverse colon is derived from the hind gut The proximal half is largely absorptive and the distal half is largely for storage The contents of the proximal half are fluid the contents of the distal half are relatively solid Carcinoma involving the right half particularly the cecum is likely to be fungating so-called colloid carcinoma with considerable mucus production whereas those in the distal half are more often of the scirrhous type

The involvement of different portions of the colon varies considerably according to reported statistics According to Henry (Rankin and Graham) the cecum is involved in 15 per cent transverse colon 10 per cent splenic flexure 6 6 descending colon 5 sigmoid 13 rectum and rectosigmoid 56 Of great importance from a diagnostic standpoint in rectal lesions is that approximately 75 per cent of these tumors are within reach of the palpating finger The lesions of the large bowel more frequently affect males than females in a ratio of about two to one

Carcinomas of the large bowel vary considerably in their gross appearance They may be divided generally into three main types (1) a large ulcerating fungating tumor with little evidence of obstruction (medullary) (2) a smaller tumor which is characterized by overproduction of fibrous tissue resulting in cicatricial contraction and early stenosis (scirrhous) and (3) a large tumor in which there is over production of mucinous material with little evidence of cellular activity (colloid)

Symptomatology —The symptoms vary considerably according to the location of the lesion There is a fundamental difference in the symptomatology of neoplasia of the right and left sides of the bowel On the right side the symptoms are those of disturbed function and there is little or no evidence of obstruction due largely to the fact that the tumor is more likely to be fungating and soft and at the same time the contents of the bowel are fluid whereas on the left side the tumor is of a cicatrizing type *i.e*

scirrhous carcinoma This together with the fact that the contents of the bowel on the left side are solid results in early obstruction The patients with large fungating ulcerating tumors on the right side may suffer from a severe anemia and have alternating attacks of constipation and diarrhea They vomit frequently, are conscious of a mass in the right lower quadrant, and occasionally have fever The cause of the anemia which can be very severe is not known but it is thought that it is commensurable with the size of the growth The anemia may be so profound that it may simulate a primary anemia In fact in every unexplained severe anemia, one should consider the possibility of a malignant disease of the right half of the colon, particularly the cecum The symptoms of right sided lesions so frequently simulate those of appendicitis that in approximately 18 per cent of cases the patient is operated upon for appendicitis In lesions on the left side there is usually increased obstipation, a history of recurrent colicky pain, and also attacks of alternating constipation and diarrhea Whereas in the majority of cases the symptoms are those of progressive intestinal obstruction occasionally the first manifestations is that of acute obstruction Distention and borborygmi are frequently associated with left sided lesions Blood and mucus may be present in the stool Tumors of the transverse colon are quite readily recognized because of their superficial location and ease of palpation

Careful examination of the abdomen and digital examination of the rectum as well as proctoscopic and sigmoidoscopic examinations should be done routinely in all patients suspected of having a malignant lesion of the bowel As mentioned above approximately 75 per cent of rectal carcinomas can be palpated on digital examination Even a lesion involving the rectum and rectosigmoid can be visualized by a sigmoidoscopic examination Sigmoidoscopic examination is of value not only in visualizing the tumor but also in permitting biopsy

In addition to proctoscopic examination roentgenography is of inestimable value in the diagnosis of colonic malignancies especially in those in and above the sigmoid The barium should be introduced under fluoroscopic observation In small tumors particularly polypi the use of the double contrast visualization *i e* barium and air is of utmost importance

Prognosis—The prognosis of carcinoma of the colon is dependent upon several factors and these may be classified as (1) those which are uncontrollable and (2) those which are controllable Under the first are the age of the patient the lesion itself and associated disease The controllable factors are the duration, preoperative and postoperative management, anesthesia operative management and complications In 718 collected cases of carcinoma of the colon, the mortality rate following resection of the right sided lesions was 19 6 per cent, whereas that following the resection of the left colon was 24 4 per cent

Treatment—The treatment of malignant lesions of the large bowel is extirpation and there are few places where surgical extirpation offers such good results as in the large bowel In a series of 4561 collected cases of carcinoma of the large bowel, 58 5 per cent were operable According to Jacobson 75 per cent of the right handed lesions 80 per cent of transverse colon lesions 63 per cent of splenic flexure and descending colon lesions and only 30 per cent of sigmoid lesions were operable The fact that carcinomas of the colon remain localized for long periods of time is demonstrated by the statistics of Larson, who found that of 210 cases of carcinoma of the colon coming to autopsy 113 had either no metastases at all or only a few regional lymph nodes which were resectable Of 3911 reported resections for carcinoma of the colon 30 7 per cent had five year cures

Certainly in the presence of obstruction some type of *decompressive operation* or *defunctionalization* is desirable The Devine defunctionating colostomy in obstructive lesions of the left colon is a valuable procedure In any case some type of decompressive procedure should be done in the presence of obstruction At present the performance of one or two stage operations has caused considerable controversy Whereas most authorities have advocated two stage operations for the left sided lesions there have been many who have thought that the right sided lesions might be done in one stage In a series of right sided malignancies reported by Allen there was a de-

crease in mortality rate from 20.5 per cent with one-stage resections to 11 per cent with two stage resections Although there are many cases in which a one stage resection can be performed with impunity it might be suggested that if there is any question about the advisability of a one stage or a two stage procedure the two-stage procedure should be chosen Whereas two stage procedures have been the method of choice in carcinomas of the colon down to the sigmoid the one-stage abdominoperineal resection has been the procedure of choice in rectosigmoidal lesions

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AFFECTIONS OF THE MESENTERY

Structural Abnormalities of the Mesentery—Variable structural abnormalities of the mesentery may occur and for the most part are due to failure or interruption of development at different embryological stages These consist essentially of abnormal lengthening or shortening of the mesentery lack of fusion or attachment to the posterior abdominal wall clefts and fenestrations and elongated folds and bands Various pathologic states may occur as a consequence of these anomalies Abnormal lengths of the mesentery permit the development of kinks and volvulus resulting in chronic recurrent partial obstruction or acute ileus and strangulation Various degrees of intestinal obstruction and strangulation may also be produced by the herniation of small loops into abnormal clefts fossae and elongated folds or bands The clinical manifestations depend upon the type and extent of the anomaly but in general are those of acute or chronic intestinal obstruction and usually appear in early life

Mesenteritis—The mesentery may become involved in the presence of general peritonitis just as the omental visceral and parietal casts are involved in the inflammatory process Rarely the inflammation is limited to the mesentery and the condition is known as mesenteritis The *etiology* is variable and may be due to tuberculous or pyogenic lymphadenitis or to extension of infection from the adjacent intestine the disease may follow accidental or operative trauma or it may be hematogenous from distant foci The *pathologic process* varies from a phlegmon or actual abscess formation to fibrous cicatricial thickening The latter referred to as chronic mesenteritis or mesenteritis retrahens appears as a hard, thickened shrunken fibrous mass with radiating cicatricial bands which tend to distort the regional segment of intestine and thus affect intestinal motility The *clinical manifestations* which are not characteristic are those of the primary disease or they may simulate various acute and chronic abdominal diseases *Treatment* is directed toward drainage of the abscess or release of intestinal obstruction

Mesenteric Hemorrhage—Spontaneous rupture of intra abdominal blood vessels with mesenteric or subperitoneal hemorrhage is extremely rare Arteriosclerosis and aneurysm are predisposing causes and hypertension is frequently present The vessels most commonly involved are branches of the

celiac axis and superior mesenteric artery The lesion consists of a hematoma which sometimes ruptures into the peritoneal cavity The condition frequently referred to as *abdominal apoplexy* is more common in males and in advanced age The *clinical manifestations* consist of sudden dull progressively increasing pain nausea and vomiting, and if the hematoma ruptures sudden exacerbation of pain shock and collapse Abdominal tenderness and rigidity are variable in degree *Treatment* is conservative or surgical depending upon the extent and rate of hemorrhage

Mesenteric Vascular Occlusion—Mesenteric vascular occlusion is relatively uncommon but probably occurs more frequently than is generally realized It may develop in either sex or at any age but the incidence is much higher in males and in advanced age groups The *etiologic factors* consist essentially of embolism and thrombosis inflammatory or degenerative processes obliterating the lumen external pressure or constriction and trauma Of these thrombosis of either arteries or veins and embolism of the arteries are the most common causes Vascular diseases such as endocarditis degenerative heart disease aortic atheromata aneurysms thrombo angiitis obliterans periarteritis nodosa arteriosclerosis especially of the mesenteric vessels are frequent predisposing causes Mesenteric venous occlusion is almost invariably due to thrombosis and peripheral sepsis and portal obstruction are the most common predisposing causes Septic processes which may contribute to mesenteric venous thrombosis include acute appendicitis puerperal infections phlebitis pelvic inflammatory disease diverticulitis and other inflammatory and suppurative processes in the peritoneal cavity Portal obstruction may result from various conditions including particularly cirrhosis of the liver hepatitis and hepatic abscess pylephlebitis and malignant diseases Rarely certain blood diseases such as polycythemia and leukemia may be the responsible factors Occasionally the condition appears as a postoperative complication especially following appendectomy hemorrhoidectomy or certain intestinal and pelvic surgical procedures Prolonged imbibition of alcohol has also been associated with mesenteric venous thrombosis Mesenteric arterial and venous thrombosis also may be produced by external pressure or constriction from abdominal tumors strangulated hernia intussusception or volvulus

Occlusion is more frequently arterial than venous and involves the superior mesenteric vessels much more commonly than the inferior The pathologic changes depend upon the extent and character of the occlusion Slow incomplete occlusions limited to a few small branches may produce little or no pathological change in the bowel wall because of the collateral blood supply On the other hand, sudden complete obstruction of the main vessels is more liable to produce extensive changes In either case the development of secondary thrombosis in the venous or arterial arcades is apparently the deciding factor and in the majority of cases leads to hemorrhagic infarction The affected bowel becomes swollen soggy and infiltrated with blood and assumes a cyanosed mottled dark red or plum colored appearance The lumen which is somewhat dilated contains altered blood The affected mesentery shows similar changes and appears thickened cyanosed and rigid The peritoneal fluid is usually increased and blood tinged Necrosis and perforation of the bowel are unusual but peritonitis resulting from transperitoneal migration of bacteria through the devitalized bowel wall is common

Symptoms—Clinically the condition is characterized by an acute onset of violent abdominal pain vomiting disturbed bowel function ileus and shock like manifestations Pain is the most constant and predominant symptom occasionally develops gradually but usually is sudden agonizing and persistent although frequently associated with severe colicky attacks Vomiting occurs early and is pronounced for the first few hours Constipation is common although diarrhea associated with tenesmus or alternating constipation and diarrhea may be present Melena is a fairly common occurrence In the acute fulminating cases shock like manifestations suggestive of internal hemorrhage are observed and the patient appears pale anxious and restless with a low blood pressure and a fast thready pulse Later the features of neglected intestinal obstruction appear The physical findings usu

ally do not conform with the severity of the symptoms Early the temperature may be normal or subnormal and later when peritonitis develops becomes elevated There is some abdominal tenderness and rigidity but distention occurs late A tumor is occasionally palpable and free fluid in the abdomen may be demonstrable The leukocytic count is always high *Diagnosis* is difficult for early in its course the condition is easily confused with acute intestinal obstruction and may resemble numerous other acute abdominal catastrophes such as intussusception volvulus acute pancreatitis and perforation of an abdominal viscus However the condition should be suspected in a patient with the predisposing factors who suddenly develops acute violent abdominal pain associated with vomiting shock low temperature high leukocytosis and melena Aspiration of peritoneal fluid has been suggested as a diagnostic procedure as the presence of a blood tinged fluid is almost pathognomonic

Treatment is surgical and consists essentially in resection of the infarcted segment of bowel and its mesentery with immediate or subsequent anastomosis depending upon the condition of the patient Blood and plasma transfusions are of inestimable value as preoperative and postoperative therapy The *prognosis* which depends upon the extent and period of involvement is usually bad the mortality ranging from 60 to 90 per cent

Mesenteric Lymphadenitis —Mesenteric lymphadenitis or lymphadenopathy has been classified into two types The specific and nonspecific The former occurs in association with certain specific infectious agents such as typhoid tuberculosis or syphilis and neoplastic diseases such as carcinoma lymphosarcoma or Hodgkin s disease In contradistinction to these forms in which the causal agent of the lymphadenopathy is known there is the type which has become recognized as a clinical entity and referred to as nonspecific mesenteric lymphadenitis because the etiology has not been definitely established

Nonspecific mesenteric lymphadenitis occurs more commonly than is generally realized The sex incidence is greater in females and the age incidence is highest between five and fifteen years The ETIOLOGY is controversial and among the factors suggested are allergy intestinal parasites enteritis absorption of bacterial toxins and stagnant material upper respiratory infection appendicitis filtrable viruses and specific bacterial infection The two principal routes which permit involvement of the mesenteric lymph nodes are gastro intestinal and hematogenous Whereas many believe that the appendix is the portal of entry others consider the terminal ileum as the most important site of local absorption and the oropharynx as the origin of the swallowed causative agent In the Tulane Surgical Laboratory Plank investigated sixty five cases of mesenteric lymphadenitis both histologically and bacteriologically Enterococci were obtained in pure culture in 67 per cent and a gram positive diplococcus in association with colon bacilli in 27 per cent However because the agglutination reactions and vaccine tests were negative the assumption that these organisms were the definite causative agents was considered unjustified

The CLINICAL MANIFESTATIONS of nonspecific mesenteric lymphadenitis are fairly characteristic and closely resemble acute appendicitis Pain is the most constant symptom and is usually of a dull aching character localized to the right abdominal quadrant but may be colicky and referred to the region of the umbilicus or right hypochondrium The onset is frequently acute and usually of moderate severity but recurrent attacks are common Nausea and vomiting *are fairly constant manifestations but diarrhea* and constipation are infrequently observed Of the physical signs abdominal tenderness is the most characteristic and is usually located in the right lower quadrant Frequently the tenderness extends from McBurney s or Lanz s point upward and to the left along the course of the root of the mesentery It is usually of moderate severity as is also muscular rigidity Fever is characteristically of a low grade type with temperature ranging between 99° F and 100 F There is slight or moderate leukocytosis and the differential count is usually within normal limits

TREATMENT as reported by most observers has consisted of appendectomy and the follow up results have indicated that the symptoms are relieved in a high percentage of

cases In some attacks have recurred but are usually milder and tend to abate General postoperative hygienic measures such as fresh air, sunshine, adequate diet and vitamins should also be instituted

Mesenteric Solid Tumors—Mesenteric tumors may be classified into *cystic* and *solid* forms The former are about twice as frequent as the latter The primary mesenteric solid tumors arise from the connective tissue nerves and vessels between the mesenteric leaves and retroperitoneal space In the latter instance the tumor assumes its mesenteric position by pushing its way forward between the mesenteric leaves These tumors may be benign or malignant Of the benign types the most common are lipoma fibrolipoma fibroma and fibromyoma The malignant tumors include fibrosarcoma liposarcoma, neurosarcoma myosarcoma and lymphosarcoma Lipomata are the most common of all solid tumors of the mesentery The *clinical manifestations* are variable and depend upon the type, size and location of the tumors In the benign forms there is frequently only a progressive painless abdominal swelling In some there is abdominal discomfort nausea vomiting and constipation Tumors located near the bowel may produce intestinal obstruction The malignant forms are frequently associated with progressive loss of weight and anemia The mobility of these tumors is characteristic *Treatment* is surgical and consists of enucleation or removal with resection of the adjacent intestine

Mesenteric Cysts—Mesenteric cysts occur about once in every hundred thousand hospital admissions They are found at all ages but are most common in the fourth decade and the ratio of females to males is about two to one Various theories and classifications have been presented to explain their pathogenesis In general it may be stated that they are of congenital or infectious origin The *infectious types* are less common and may be due to echinococci or tubercle bacilli The *congenital forms* may be simple embryonic cysts arising from serous or chylous structures or sequestration of embryonic diverticula during the development of the intestinal tract such as Meckel s diverticulum or they may be neoplastic arising from misplaced ovarian tissue (dermoids and teratomas) or from other urogenital tissue such as the wolffian duct and body and the mullerian body in the retroperitoneal area or from the entoderm (enterocystoma) They vary in size considerably and may be unrecognizably small or huge tumors which fill the abdominal cavity Their location also varies but they are found most frequently near the lower jejunum and ileum Pathologically the cysts are usually unilocular, although occasionally multilocular and have a fibrous wall which may contain bundles of smooth muscle, giant cells and lymph follicles Occasionally the cysts connect with the intestinal lumen by a duct The contents of the cysts vary from a clear mucinous material to a yellowish milky brown or sanguineous fluid Rarely the cysts undergo malignant degeneration

The *clinical manifestations* are variable and there are no pathognomonic features The *symptomatology* depends upon the complications produced by the cysts the most frequent of these being intestinal obstruction This may be of acute onset but usually there is a history of repeated attacks of nausea, vomiting and colicky pain associated with chronic constipation and loss of weight and strength Other complications consist of rupture with consequent peritonitis and hemorrhage into and torsion of the cyst.

Diagnosis is rarely made preoperatively but the condition should be suspected in the presence of a freely movable and cystic abdominal tumor associated with colicky pain and other manifestations of intestinal obstruction Occasionally roentgenographic studies are of value in delineating the cyst

Treatment is essentially surgical with enucleation as the procedure of choice In some cases because this is not feasible or because of strangulation or malignant degeneration intestinal resection with removal of the cyst bearing area of the mesentery is necessary

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DISEASES OF THE LIVER

INTRODUCTION

The liver is probably the most important single glandular structure in the body Without it neither man nor any of the higher animals can survive more than a few hours Its known functions are numerous and doubtless others will be discovered Among the more important of these functions may be listed glycogen storage regulation (in conjunction with the pancreas suprarenals and central nervous system) of the blood sugar levels regeneration of the serum protein and the regulation of the albumin globulin ratio the manufacture and secretion of bile which in turn aids in fat digestion the production and storage of prothrombin and of the antianemic factor which regulates the maturation of red blood cells in the bone marrow the production of urea from amino acids and other detoxifying powers as for example in the acetylation of the sulfonamides and the synthesis of hippuric acid brought about by the conjugation of benzoic acid and glycine

It would be reasonable to expect that an organ charged with so many duties should be vulnerable to attack from many quarters and by various agents That this assumption is correct is borne out by the number of clinical conditions in which the liver would seem to be the principal organ affected It would be reasonable also to expect that the functions of this organ might be deranged by such attacks in varying degree and possibly in a selective manner That this is indeed the case is indicated by the results obtained in experimental and clinical studies employing the various tests designed to measure such functions One test (or several) may show impaired function while others yield normal values Presumably this is because the disease has not impaired all the functions of the liver equally The main difficulty in interpreting liver function tests would seem to lie in the fact that the liver possesses an enormous factor of safety and therefore a large proportion of the hepatic tissue must first be put out of action by disease before abnormal results can be expected in these tests Nevertheless, some progress is being made along these lines, and in the subsequent discussions of the various diseases of the liver an attempt will be made to indicate where function tests may be expected to aid in diagnosis or in estimating the degree of damage suffered by the organ The student is cautioned however against a too ready acceptance of the results of laboratory procedures and is urged to apply himself to the clinical examination and the evaluation of symptoms and physical signs the mastery of which is still most important in the study of hepatic disease

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JAUNDICE

(*Icterus*)

Jaundice is a condition characterized by a yellowish staining of the skin mucous membranes and body fluids with bile pigment It is not a disease but must be regarded as a symptom with varying etiology and significance Jaundice is of three types (1) obstructive hepatic jaundice (2) hemolytic (or nonobstructive) jaundice (3) toxic or infective hepatic jaundice

The old idea that the bile pigment is manufactured or transformed in the hepatic cells has been generally discarded It is now believed that the bile pigment is formed

by the cells of the reticulo endothelial system from particles of hemoglobin liberated by disintegration of red blood cells

In the writer s opinion, the most plausible explanation of the causation of jaundice is that proposed by McNee He points out that under normal conditions the small quantity of bile pigment formed from the normal disintegration of red blood cells is carried by the hepatic artery and portal vein in the liver lobule passes through the polygonal cells of the liver into the bile capillaries and is excreted into the intestine Part of this is reabsorbed as urobilinogen and the remainder is excreted with the feces

According to this conception jaundice will occur under the following circumstances (a) when the bilirubin (bile pigment) passes through the polygonal cells in the normal manner but on reaching the bile ducts meets with obstruction (stone neoplasm etc) and has to be reabsorbed into the blood stream (b) when through toxic or infectious processes the polygonal cells are damaged and no longer able to deal with the bilirubin brought to them the bile simply passes on into the systemic venous circulation by way of the hepatic vein (c) when the rate of blood destruction results in the presence of excessive amounts of bilirubin in the blood the normal polygonal cells are unable to cope with it and allow a quantity to pass on into the general circulation (hemolytic jaundice) It is to be expected that certain clinical conditions will involve both (a) and (b)

By utilizing Ehrlich s diazo reaction van den Bergh developed a test for bilirubin in the blood This test indicates two forms of bilirubin A *direct* or *immediate* reaction is believed to indicate bilirubin which has passed through the polygonal cells and therefore is obtained in pure obstructive jaundice An *indirect* or *delayed* reaction indicates bilirubin which has not been passed through the liver cells and hence is found in hemolytic jaundice There is evidence to suggest that this type of bilirubin is bound to the plasma proteins and therefore does not pass through the kidneys into the urine In toxic or infective jaundice both forms of bilirubin are present hence a *biphasic* van den Bergh reaction The test is thus an excellent theoretical method of differentiation provided it is interpreted with the reservation that pure types of jaundice practically never occur

A van den Bergh test showing up to 0 6 units of bilirubin in the blood is considered normal Amounts up to 4 units may be present without visible jaundice (*latent jaundice*)

Obstructive Jaundice —*Etiology*—Obstructive jaundice comprising about 85 per cent of all cases may be caused by any of the following conditions

(*a*) Obstruction of the ducts from within by gallstones, inspissated bile and mucus or parasites

(*b*) Obstruction due to changes in the *walls of the ducts caused by inflammatory* swelling (cholangitis) new growths of the ducts stricture and possible spasm (Spasm has been suggested as a probable cause of so called ' emotional jaundice ')

(*c*) Obstruction of the ducts from without by pressure from new growth cysts gummata enlarged glands and adhesions and rarely by

(*d*) Kinking or torsion of the ducts which is said to be the result of displacement of the liver, stomach or right kidney

Symptoms and Signs —The symptoms and signs may be conveniently grouped according to the system involved

(*a*) Skin and Mucous Membranes —The conjunctivae first show the *yellow pigmentation* which soon appears in the skin of the entire body Care must be taken not to mistake for *jaundice the* yellowish discoloration caused by patchy masses of fat in the conjunctivae Artificial light cannot be depended upon to reveal the presence of a slight icteric tinge The color may vary from a pale yellow to a deep olive green In black jaundice the color is a greenish black and is said to be due to oxidation of the bilirubin to biliverdin

Pruritus or itching is usually present especially in chronic cases *but may* be entirely absent even when jaundice is marked Preicteric pruritus probably is not as Riesman thought suggestive of carcinoma

Eruptions on the skin are sometimes observed They may be of petechial purpuric or nodular (xanthomata) character The latter are rare and most often affect the eyelids hands and feet

(*b*) Body Fluids and Excretions —The urine varies in color from light yellow to brownish green It sometimes becomes icteric before discoloration of the skin is visible Gmelin s nitric acid test distinguishes bile pigments from blood pigment santonin etc Traces of albumin and bile stained casts are often present when jaundice is persistent or severe If obstruction of the bile ducts is complete little or no urobilin appears in the urine but if it is only partial this substance is present in normal or even increased quantities Bile salts are found with the bile pigments but because of their greater diffusibility may disappear from the urine (dissociated jaundice)

Blood —Before the bile pigment reaches the urine it must of course appear in the blood plasma The early discoloration which this produces may be of diagnostic importance when the color of the skin and sclerae is doubtful French observers have called attention to instances in which the bile salts associated with bile pigment in the blood pass into the intestine and leave the pigment behind (dissociated jaundice) Brule states that under such conditions the usual minute particles of fat (hemokonia) appear in the plasma after meals whereas when obstruction is complete this does not occur

In long standing and severe jaundice the clotting time of the blood is markedly prolonged and operations are often complicated by obstinate hemorrhage This is due to a deficiency of prothrombin in the blood and may best be obviated by the use of vitamin K together with bile salts and by transfusion of blood

Jaundice alone does not increase the leukocyte count but if prolonged may reduce the red cell count The phosphatase content of the serum is increased in obstructive jaundice normal in hemolytic jaundice and too variable in catarrhal jaundice to be of diagnostic value

Cerebrospinal Fluid Tears Sweat and Others —Tears saliva and milk are seldom stained but the sweat is often markedly tinted All tissues of the body except the central nervous system are discolored The cerebrospinal fluid is usually unaffected

(*c*) Cardiovascular System —In early uncomplicated jaundice the heart rate is slow and may be irregular The bradycardia which is due to the action of bile salts upon the cardio inhibitory mechanism may be counteracted by full doses of atropine

(*d*) Gastro intestinal System —The most striking feature of the gastro intestinal system is the change in the color of the stools Their clay colored appearance is produced by three factors the absence of bile the presence of undigested fat in quantities which according to Muller may be increased from the normal 10 per cent to 55 per cent or more and the presence of bubbles of gas which results from putrefaction caused by intestinal indigestion

Constipation often occurs as well as anorexia nausea and flatulence The liver is usually enlarged and the gallbladder is sometimes distended If the obstruction is due to a calculus in the common duct however the gallbladder is usually small because of previous inflammation (Courvoisier s law)

(*e*) Nervous System —There is usually mental depression headache drowsiness and languor In severe cases or in late stages the nervous symptoms may be very severe and consist of delirium stupor or coma (cholemia) Yellow vision so called xanthopsia is sometimes complained of and is due to pigmentation of the vitreous humor

The diagnosis prognosis and treatment of the various forms of obstructive jaundice are described under the headings of the conditions responsible

Hemolytic Jaundice (*Hematogenous Jaundice Nonobstructive Jaundice Chronic Splenomegalic Hemolytic Jaundice*) —Hemolytic jaundice is generally regarded as of splenic origin and is described in the section on Diseases of the Spleen

Toxic and Infective Jaundice —Jaundice of toxic or infectious origin is a symptom of some condition such as cinchophen phosphorus chloroform dinitrophenol or arsphenamine poisoning pneumonia septicemia Weil s disease syphilis or certain obscure intoxications The more important of these will be considered separately In all cases of toxic and infectious jaundice there is evidence of damage to liver parenchyma

Catarrhal Jaundice (*Acute Infectious Hepatitis Acute Infectious Jaundice Epidemic Jaundice*) —Definition —An acute

hepatic inflammation characterized by gastric upset and jaundice

Etiology.—The exact cause is unknown. More than half the cases occur in the school age group although the disease is encountered throughout adult life. Multiple cases are frequently seen in households and in schoolrooms. Epidemics of varying degree are not uncommon.

Morbid Anatomy.—The older conception of this disease was that it was primarily a duodenitis and cholangitis, the latter interfering with the excretion of bile with consequent absorption into the blood stream. It is now believed that in the majority of cases if not in all there is primarily an acute hepatitis with secondary involvement of the bile ducts. The liver is enlarged, smooth and greenish in color. A study of biopsy specimens reveals definite degenerative and necrotic changes in the liver lobules. The epithelium of the bile capillaries shows cloudy swelling, leukocytic exudation and epithelial desquamation. The bile is more viscid than normal and contains desquamated epithelial cells. Sometimes pus cells are also found.

In the more severe cases these changes approach in degree those found in subacute yellow atrophy or even the acute form. These pathologic findings, together with clinical experience in the rare instances where an apparently mild catarrhal jaundice develops into a condition indistinguishable from acute yellow atrophy of the liver, have led to the suggestion that these diseases have a common basis.

Symptoms and Signs.—The onset is usually insidious although in epidemics it may be sudden. There is general malaise with headache, anorexia, often nausea and vomiting, a feeling of epigastric fulness and distress. Fever is usually moderate, from 99° to 101° F, but may be higher and accompanied by chills. The bowels are apt to be constipated but there may be diarrhea. During this stage, which may last from one to three days, a tentative diagnosis of influenza is frequently made.

Not infrequently the symptoms decrease after twenty four to forty eight hours, only to be followed on the third or fourth day by the appearance of jaundice which steadily increases. In the severer cases the systemic symptoms return or become more marked and in rare instances there may be delirium and coma.

As a rule, the fever soon disappears and the lethargy and prostration lessen. The tongue is coated, the urine is very dark and the stools usually are clay colored. The pulse tends to be slow, the liver is enlarged and tender, and the spleen is usually palpable. No significant changes are found in the red or white blood cells. The van den Bergh test is biphasic and the quantitative form of this test, or the icteric index, is useful in following the course of the disease. Bile is present in the urine, but, if the stools are clay colored, there is no urobilinogen. There may be a trace of albumin and a few casts.

Itching of the skin may be a prominent feature and is not necessarily proportionate to the degree of jaundice. Both usually disappear gradually in the course of three or four weeks. Epidemic cases are frequently mild and recovery may occur in two weeks. While the jaundice may persist for six or eight weeks, the physician should consider the possibility of some other cause where the bilirubin content of the blood does not show a decrease in thirty days. Cases have been reported in which cirrhosis of the liver finally ensued.

Diagnosis.—In the young, there is rarely any difficulty in diagnosis. The mode of onset is of importance in differentiating this disease from obstructive jaundice or from infectious diseases such as pneumonia, Weil's disease and so on. One should keep in mind the possibility of an exacerbation in a case of hemolytic icterus.

In patients more than forty years of age the possibility of carcinoma of the head of the pancreas or of the biliary tract must always be considered. An insidious and painless onset should arouse suspicion. Gall stones in the common duct may easily be confused with any of these conditions and where serious doubt exists, laparotomy should be performed.

The possibility of a progressively severe case developing into the clinical picture of acute yellow atrophy should be borne in mind but should not be overlooked if careful watch is kept of the size of the liver.

Finally, the possibility of syphilis should not be forgotten. Where arsenicals have been

administered a toxic hepatitis may be pro duced

Treatment —During the acute phase the patient should be kept in bed The diet should consist mainly of carbohydrates but since there is evidence that proteins are required for liver regeneration, skimmed milk should be given in reasonable quanti ties Fats of course are poorly digested owing to the deficiency of bile in the intes tinal tract and should be kept at a mini mum Where nausea and vomiting are severe 5 per cent glucose in saline should be given intravenously in amounts of 2 000 cc per twenty four hours and food by mouth discontinued After the acute symptoms have subsided the diet may be en larged to include vegetables and fruits chicken and scraped beef A normal diet is gradually resumed as the jaundice dis appears

The bowels should be regulated with salines if necessary The total fluid intake should approximate 2500 cc daily The itch ing may be relieved by the application of calamine lotion but very often is difficult to control The slow intravenous injection of 5 cc of a 10 per cent solution of calcium gluconate will often give temporary relief

Cinchophen Poisoning—Owing to the widespread use of this drug in arthritic con ditions it is perhaps the most common chemical cause of toxic hepatitis Fortu nately relatively few individuals have an idiosyncrasy for cinchophen but those who are very susceptible may have serious conse quences from a single dose Others show signs only after continued use of the drug

Morbid Anatomy —Postmortem exami nation reveals a condition resembling acute yellow atrophy In a few of those who re cover there is a progressive fibrosis leading to the clinical picture of cirrhosis

Symptoms and Signs —Jaundice is a constant feature General malaise and gas tro intestinal disturbances are usual These symptoms may be transitory with early re covery On the other hand they may in crease the jaundice becoming intense the patient stuporous and dying in coma At the onset fever may or may not be present but in unfavorable cases there is a high fever before death

At first the liver may be enlarged but soon decreases in size There is oliguria, much bile in the urine and albumin is present

Moderately severe cases run a protracted course and complete recovery is not uncom mon A few subsequently develop cirrhosis of the liver

Diagnosis —This depends entirely on the history The taking of cinchophen (or of some patent rheumatism remedy contain ing cinchophen) is essential to the diagno sis

Treatment —There is no specific remedy The treatment is the same as for acute yel low atrophy (*q v*)

Phosphorus Poisoning—Pathogenesis — Wells has shown that the hepatic cells are killed by phosphorus and that liberation of their autolytic ferments leads to extensive breaking down of the liver As a result leu cine tyrosine cystine and sarcolactic acid are present in the blood and urine

Morbid Anatomy —All the organs under go fatty change but the liver seems es pecially damaged It becomes large friable and yellow Occasional small hemorrhages are seen Microscopically the hepatic cells show marked fatty infiltration and degen eration of the cytoplasm

Symptoms —Evidences of severe gastro intestinal irritation usually appear soon after the poison is taken Intense nausea vomit ing burning epigastric pain and profound collapse are the usual symptoms Should the patient live two or three days evidences of hepatic damage appear such as enlargement and tenderness of the liver and spleen jaundice and vomiting of grumous material (hemorrhage from mucous surfaces) Later drowsiness delirium and coma supervene and death ensues in a day or two In some patients the course is more subacute and recovery takes place

Diagnosis —A history of the ingestion of phosphorus with suicidal intent or by acci dent is important Match heads or rat paste are sometimes used The occurrence of severe gastric disturbances before the onset of jaundice is suggestive Phosphorus poison ing differs from *acute yellow atrophy* in that the liver is enlarged and the odor of the vomitus is characteristic

PROGNOSIS —The mortality is high when the hepatic involvement is marked, but many cases run a chronic or subacute course and end in recovery

TREATMENT —In the early stages gastric lavage with an oxidizing agent (peroxide of hydrogen 1–3 per cent) or old turpentine (3 cc in emulsion) is an important form of treatment The diet also is important The protein intake especially as regards meats should be strictly limited and the carbohydrate should be increased proportionately During the acute stage this can be given in the form of glucose either by mouth or intravenously Insulin, 10 units hypodermically three times a day, combined with a carbohydrate diet or with intravenous glucose has been recommended by various authors

Arsphenamine Poisoning —Whether or not the jaundice which has been observed to follow the intensive administration of arsenicals in the treatment of syphilis is sometimes a manifestation of syphilis and not the result of treatment it is certain that a severe type of toxic jaundice resembling a subacute form of acute yellow atrophy has been caused directly by such medication In this the liver is reduced in size The *symptoms* vary from a mild grade to those of acute yellow atrophy with death Strathy has called attention to the acuteness of the cardiohepatic angle as demonstrated by x ray Bailey and McKay suggest that mercury may be an etiologic factor in some instances and that the disturbance may be of the nature of a 'Herxheimer reaction in the liver The *treatment* of the condition is partly dietetic and partly medicinal The diet should be very light and relatively rich in carbohydrates Sodium thiosulfate (0 75–1 5 Gm in 15 cc freshly distilled water) is given intravenously once a day for ten days to render the arsenic in the liver and other tissues insoluble and thus retard its excretion and toxic action

Icterus Neonatorum —Jaundice of the newborn may conveniently be divided into two types (*a*) the mild form from which recovery is usual and (*b*) the severe form which usually proves fatal

The *mild type* occurs in about one third of all infants and while most commonly seen in hospitals is not infrequently encountered in private practice It is believed that this form of jaundice is hemolytic in nature being the result of a physiologic readjustment of the circulation after birth The jaundice appears about the second or third day and lasts a week or more The stools contain bile pigment but the urine does not The condition is symptomless the prognosis good, and treatment unnecessary

A rare form of mild catarrhal or infectious jaundice is caused by acute duodenitis This does not differ materially from the catarrhal disease of older children

The *severe jaundice* of the newborn is of three types (1) that due to definite *obstruction* such as congenital absence of the bile ducts syphilis of the liver or of the bile duct, and gallstones These conditions are dealt with elsewhere

(2) That caused by *thrombophlebitis* or *suppurative phlebitis* in which the infection begins at the umbilicus and extends along the umbilical vein This sometimes develops into general septicemia The pathology of the disease is that of septicemia or pyemia namely cloudy swelling of the tissues abscesses and bronchopneumonia

The jaundice appears about the fifth day with remittent fever rapid pulse and respiration vomiting diarrhea and umbilical or gastro intestinal hemorrhage the infant at first restless becomes comatose and dies

Treatment consists in the administration of enemata and minute doses of calomel as an intestinal antiseptic Antistreptococcic serum has been recommended as the *Streptococcus haemolyticus* is usually the infecting organism Sulfanilamide has now become the drug of choice

(3) *Familial jaundice of the newborn* This type of jaundice exists at the time of birth or appears soon afterward and usually affects successive infants The child soon becomes drowsy and may die in convulsions At *autopsy* the organs appear bile stained all tissues except the cortex of the brain being affected Petechial hemorrhages occur in the viscera the spleen and liver are enlarged The *prognosis* is bad Rolleston recommends administration of sodium salicylate and hexamine to the mother as a *prophylactic measure* and *treats* the infant with minute doses of calomel

The hemorrhagic tendency may be prevented by giving the mother 0 6 mg naphthoquinone (synthetic vitamin K) four times a day for two or three days prior to confinement It may also be given therapeutically to the child

Acute Yellow Atrophy —*Definition* — Acute yellow atrophy is an acute diffuse necrosis of the liver cells as the result of intoxication or infection and is characterized by a progressive diminution in the size of the organ jaundice and profound toxemia

Etiology —The condition is rare Rolleston states that he has seen it only thirteen times in thirty four years except when it was due to definite agents such as arsphenamine trinitrotoluene etc The disease is said to develop more often since the introduction of these chemicals into common use It occurs in individuals of all ages but most frequently in the third decade of life Women suffer from it more often than men probably on account of pregnancy the toxemia of which appears to be definitely related to that of acute yellow atrophy Certain infections such as syphilis are sometimes held responsible In cases associated with lues it is often difficult to determine whether the syphilitic infection or the arsphenamine treatment has brought on the condition There are cases reported however in which the jaundice of the early stage of syphilis developed into acute yellow atrophy without administration of arsphenamine Alcoholism has been followed in a few instances by acute yellow atrophy Probably any condition which leads to impairment of the resistance of the liver cells may be of etiologic significance Preexisting disease of the liver is sometimes a factor

Pathogenesis —The resemblance of the condition of the liver in acute yellow atrophy to that in various forms of poisoning (phosphorus and chloroform) indicates that the probable cause of the changes is to be found in some form of toxemia which damages the liver cells and results in subsequent autolysis and destruction It is thought that the jaundice is due to obstruction of the smaller bile ducts by viscid secretion and desquamated cells MacCallum suggests that it follows degeneration and consequent obliteration of the bile capillaries

Morbid Anatomy —The liver is greatly diminished in size the weight often being reduced to one half or one third of normal The surface appears shrunken and wrinkled The atrophy may be more advanced in the left lobe The color is yellowish green and in some areas dark red On section the liver is yellowish and contains scattered depressed areas of reddish color These are the more seriously degenerated portions When atrophy is subacute raised areas of yellowish or greenish color may be seen which are due to compensatory regeneration The marking of the lobules is indistinct especially in the red areas The liver tissue is soft and friable The bile ducts contain mucus only and the gallbladder may be empty or contain a small amount of bile

Microscopically there is such widespread degeneration of the liver cells that it is difficult to recognize the organ The lesions are more advanced in the reddish than in the yellow areas The cells are in all stages of necrosis They first become granular and bile stained then fragmentary degeneration takes place in the nuclei which soon lose their staining power In certain regions particularly around the central veins where the cells appear to undergo complete destruction only the debris and the fibrous and vascular framework of the organ can be seen The increase in fibrous tissue in such cases is only apparent Hemorrhages occur here and there between the cells

In the subacute cases the surviving liver cells at the periphery of the affected areas and the cells of the interlobular bile capillaries show evidence of compensatory regeneration (hyperplasia) This and the regeneration of the liver cells results in the formation of areas or nodules which stand out from the surrounding shrunken tissue If the disease does not rapidly prove fatal fibrotic changes may take place in the interstitial tissue (cirrhosis) Chemical investigation shows the presence of amino acids particularly leucine tyrosine and other substances the products of autolysis and destruction of the cells of the liver The quantity of fat is not increased the yellow color being due to bile

The other organs are stained with bile and often contain hemorrhages The spleen is enlarged in about half of the cases The epithe-

lium of the kidneys undergoes granular degeneration and the myocardium is softened

Symptoms—At the *onset* the symptoms are those of benign catarrhal jaundice and may in no way indicate the seriousness of the condition Most commonly this stage lasts for five or six days but in some instances—notably in syphilitic cases—persists for as long as three weeks

The *second stage* sets in abruptly with grave symptoms Severe headache restlessness, delirium, vomiting, convulsions transient paralysis, and dilatation of the pupils, which are among the prominent features, are indicative of marked toxemia and irritation of the nervous system The jaundice becomes deeper Hemorrhages may occur into the skin or from the mucous surfaces Abortion may occur The temperature usually remains low but may rise suddenly before death The disease proves fatal a few days after the onset of the severe symptoms usually after the development of coma and stertorous breathing

The liver begins to diminish in size at the onset of the second stage It becomes flabby falls away from the anterior abdominal wall and is replaced by coils of the intestine Consequently, it is extremely difficult to ascertain the exact size of the liver by percussion, because the hepatic area is tympanitic Strathy and Gilchrist point out that the cardiohepatic angle, as seen by x ray examination becomes more acute as the atrophy progresses The spleen is usually enlarged

The urine which is scanty, becomes markedly bile stained and contains albumin and casts The quantity of urea is diminished and the ammonia nitrogen content increased probably by failure of the liver to convert ammonium compounds into urea or as the result of acidosis and the fixation of ammonia by organic acids Leucine and tyrosine crystals are usually present The coagulation time of the blood is prolonged There may be moderate leukocytosis

Diagnosis—The important diagnostic features of this disease are the jaundice marked cerebral symptoms in the second stage and the progressive diminution in the size of the liver The latter point serves to distinguish acute yellow atrophy from such other forms of severe jaundice as *Weil's disease* and *phosphorus poisoning* In severe *trinitrotoluol poisoning* the liver also atrophies, but the history of exposure determines the diagnosis and is easily obtained

The line of demarcation between the clinical picture of acute yellow atrophy of the liver and that of cases not so violent in nature is less distinct than has been supposed The clinical and pathologic records of any large hospital contain cases which seem to occupy a borderline position between acute yellow atrophy and benign catarrhal jaundice

Prognosis—The disease usually proves fatal after about two weeks Occasionally the course is more subacute and the illness lasts several weeks Recovery is known to take place but is followed by the appearance of signs of cirrhosis of the liver The prognosis in pregnant women is invariably bad

Treatment—Rolleston suggests that as a prophylactic measure chloroform should never be given to jaundiced pregnant women, and that mercury should be used in treating the benign jaundice of early syphilis

The treatment of acute yellow atrophy is entirely symptomatic The toxemia is combated by subcutaneous or intravenous injection of large amounts of saline solution with 5 per cent glucose Insulin may be tried after the manner described in the treatment of phosphorus poisoning Intestinal antisepsis and purgation are advised Plenty of water with sugar should be given to combat the acidosis Bismuth may be used to relieve vomiting The diet should consist largely of cereals and milk

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AFFECTIONS OF THE BLOOD VESSELS OF THE LIVER

Hyperemia may be either active or passive

Active Hyperemia or Congestion—Active hyperemia is physiologic during digestion Pathologically it results from (1) overeating alcoholism and other dietary indiscretions (2) sedentary habits (3) infections such as typhoid fever malaria and yellow fever (4) true nonsuppurative hepatitis and (5) constipation

MORBID ANATOMY—Since it is only in the infective type that there is opportunity for postmortem study of the liver little if any accurate knowledge of the pathology of this condition is available The liver is said to be uniformly congested and swollen The hepatic cells suffer little if any change

SYMPTOMS—The symptoms are a sense of fulness in the right hypochondrium headache malaise depression and indefinite digestive disturbances such as anorexia flatulence and constipation Objectively the liver is tender and slightly enlarged The sclerae are often muddy and the complexion sallow

TREATMENT—Prophylaxis consists in the avoidance of habits which predispose to the condition The actual *treatment* of the condition should consist of rest in bed marked reduction in the food intake and free purgation with calomel and salts Hot compresses poultices or mustard plasters over the liver give subjective relief After a few days the diet may be increased the patient allowed to get up and to undertake moderate exercise gradually The condition is not serious in itself and under treatment seldom lasts more than a few days

Chronic Passive Congestion—ETIOLOGY—Chronic passive congestion is very common and usually results from back pressure of blood from the right auricle in mitral stenosis or insufficiency or in chronic myocardial disease Rarely it is due to obstruction of the flow of blood from the venae cavae into the right auricle by enlarged lymph nodes mediastinal tumors or other intrathoracic abnormalities such as pulmonary emphysema fibroid lung chronic pleurisy and adherent pericardium

MORBID ANATOMY—The liver is usually markedly enlarged and engorged with blood In long standing cases structural changes always take place On section the cut surface is peculiarly variegated the dark red central portion of the lobule being surrounded by a grayish or yellowish zone which produces an appearance not unlike that of the cross section of a nutmeg hence the familiar term *nutmeg liver* Microscopic examination reveals distention of the central veins which are surrounded by shrunken poorly staining cells (pressure atrophy) and small hemorrhagic areas The cells in the outer zones of the lobules (the lighter area) are cloudy or fatty Whether pressure atrophy completely accounts for the condition of the cells in the central zone of the lobule is not certain Some pathologists emphasize the fact that the central cells are farthest from the food supply and

suffer first from starvation and lack of oxygen

When passive congestion of the liver persists for years the content of connective tissue increases particularly within the lobule (*cardiac cirrhosis*) *It is doubtful whether* this is a true cirrhosis for it seems more probable that when the liver cells atrophy the normal stroma of the liver remains and appears to comprise a greater proportion of the tissue

SYMPTOMS—The symptoms are mainly those of the associated cardiac or other underlying causes Those directly referable to the liver are pain and tenderness and a feeling of fulness over the right hypochondrium Vague digestive disorders are common and there may be slight jaundice Portal obstruction with ascites may occur before general cardiac dropsy develops The liver is enlarged tender and firm In a small proportion of cases especially in those with tricuspid insufficiency pulsation is felt

DIAGNOSIS is rarely difficult but, if the causal lesion be overlooked the large tender liver may be suspected of harboring an *abscess* If the patient be studied with particular reference to the condition of the circulation this affection as well as those of *cirrhosis hepatitis new growth* and *fatty and amyloid liver may easily be ruled out*

PROGNOSIS—The prognosis is that of the causal condition

TREATMENT—In determining the type of treatment the underlying cause is paramount Direct hepatic therapy is seldom necessary Calomel and other cathartics may be given to deplete the portal circulation

Portal Thrombosis (*Pylethrombosis Pylephlebitis Adhesiva*) —*Etiology*—Portal thrombosis occurs most commonly in cirrhosis of the liver and when malignant growths penetrate the portal vein It is also encountered occasionally in syphilis of the liver and in association with infective processes in the vicinity such as cholangitis appendicitis, and peptic ulcer Sohval calls attention to its occurrence in polycythemia vera It is said to be due in rare instances to primary portal endophlebitis

Diagnosis—The diagnosis is exceedingly difficult and in most cases is not made In a patient with hepatic cirrhosis or intra abdominal malignancy the sudden onset of ascites with other evidence of engorgement of the portal branches (hematemesis melena splenomegaly) should suggest portal thrombosis If thrombosis takes place gradually, diagnosis is impossible

Treatment is unsatisfactory, particularly in the acute cases It should be designed to relieve symptoms In *syphilitic* cases appropriate therapy is said to be of use in the earlier types The acute form usually proves rapidly fatal Recovery depends upon the establishment of an efficient collateral circulation with ultimate fibrosis of the portal vein (*pylephlebitis adhesiva*)

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THE CIRRHOSES OF THE LIVER

For practical purposes it is convenient to divide the cirrhoses of the liver into two main classes portal and biliary The term cirrhosis which was first applied by Laennec refers to the tawny color of the surface of the liver in the commoner (portal) type but it has since by common usage become synonymous with fibrosis

Portal cirrhosis includes besides ordinary portal cirrhosis (the atrophic cirrhoses of Laennec) certain less common forms namely (1) the form associated with splenomegaly in Banti's disease (2) portal cirrhosis with progressive lenticular degeneration (Wilson's disease) and (3) the cirrhosis of hemochromatosis These are described elsewhere Of the biliary type there are two varieties Hanot's hypertrophic biliary cirrhosis and the obstructive biliary cirrhosis of Charcot

Portal Cirrhosis (*Laënnec s Cirrhosis Atrophic Cirrhosis Alcoholic Cirrhosis Chronic Hepatitis Hobnail Liver Gin drinker s Liver*) —*Definition* —Portal cirrhosis is a chronic disease characterized by degeneration of liver parenchyma and by periportal fibrous tissue proliferation with resulting distortion of the normal lobular pattern

Antecedent Factors —Portal cirrhosis is a disease of late middle life occurring generally between the ages of thirty five and sixty five with a peak incidence at about fifty five years Men are affected more often than women (2 to 1) Occasionally it is seen in children The incidence of this disease is high in certain countries of the Orient and Near East namely India Northern China East Indies and Syria In these regions cirrhosis has been attributed to associated diseases such as malaria dysentery and intestinal parasites In the Western Hemisphere portal cirrhosis is associated commonly with alcoholism which occurs in 50 to 85 per cent of cases in various reported series Consequently this disease is seen in occupational groups which enjoy ready access to alcoholic liquors The incidence of syphilis is relatively high (15 to 25 per cent) Many such patients however receive treatment with arsenicals which are known to injure the liver There is little evidence that hereditary or constitutional factors play a significant role

Etiology —Cirrhosis of the liver probably represents a reaction to injury that can be caused by a variety of agents some of them known and others unknown Therefore it is doubtful that a single etiologic factor accounts for all instances of the disease Parasitic infestations (*e g* schistosomiasis) may produce portal cirrhosis Certain instances of unresolved acute hepatitis or "catarrhal jaundice" may develop portal cirrhosis A relatively small number of cases result from poisons such as carbon tetrachloride cinchophen phosphorus and arsenic Although syphilis malaria and thyrotoxicosis have been classed as etiologic agents it seems more likely that they play a contributory or secondary role



Fig 77—Liver showing portal cirrhosis (Courtesy of Professor William Boyd)

In recent years interest has been directed at the alcoholic or Laennec type of cirrhosis which comprises the large majority of cases Clinical and experimental studies strongly suggest that a direct relationship exists between nutritional deficiency and the development of portal cirrhosis Whether alcoholism in this disease simply predisposes to the dietary deficiency (as in alcoholic pellagra

and beriberi) or whether it lends an added toxic effect is not clearly established

Morbid Anatomy and Pathogenesis — While the liver is usually smaller than normal, because of the contraction of the fibrous tissue and atrophy of liver cells, it is often enlarged, especially when there is much fatty change This 'fatty cirrhotic liver' is usually smooth and yellowish white not unlike that of the ordinary fatty liver but its texture is firm and the tissue cuts with resistance on account of the increased quantity of connective tissue in the portal areas In the ordinary type the surface is granular with elevations or "hobnails" the size of which varies from that of a pinhead to that of a pea or bean It is greenish yellow in color and surrounded by a greenish white depression (contracted fibrous tissue) The elevated areas are islands of regenerated liver cells which are constantly present or lobules or portions of lobules of original liver tissue On section the surface appears variegated small areas of greenish yellow or yellowish-brown being surrounded by grayish white bands of fibrous tissue The yellowish areas correspond to the elevations on the capsular surface and therefore represent the normal or hyperplastic liver tissue

Microscopically the fibrotic changes are seen to involve the portal areas In certain parts the fibrosis may be unilobular and enclose only a very small area of liver tissue but more often groups of lobules are enclosed together The liver lobules themselves are distorted or atrophied, the central vein coming to occupy an eccentric position because the degenerative changes are more marked on one side of the lobule than the other The hepatic cells may show changes of a hyaline nature in the early stages, and fatty changes are very prominent *Pigmentation* of the cells with bile and hemosiderin may be noted The latter is hematogenous in origin and may be associated with similar pigmentation in the skin and pancreas This condition is most often associated with diabetes to which the name *bronzed diabetes* is given In certain areas evidence of regeneration of the parenchyma is to be seen in the shape of new cells of large size arranged in nodular masses near the periphery of the lobule where the blood supply is most abundant The portal areas also show evidences of proliferation of the cells of the bile ducts (pseudobile canaliculi) and contain numerous well formed blood vessels derived from the hepatic artery



Fig 78 — Microscopic appearance of liver in portal cirrhosis (Courtesy of Professor William Boyd.)

The most conspicuous feature however whether on macroscopic or microscopic examination is the tremendous increase in the fibrous tissue of Glisson s capsule on the

liver surface and throughout its ramifications along the portal radicles The obvious result is a marked obstruction of the portal circulation Evidence of an attempt to overcome this by establishing an efficient collateral circulation is easily demonstrated (1) the veins at the lower end of the esophagus anastomose with the coronary vein of the stomach and form large varicose trunks (2) the inferior mesenteric veins anastomose with the hemorrhoidal veins and often give rise to well marked hemorrhoids of clinical importance (3) anastomoses form between the epigastric and portal veins by way of the para umbilical vein of Sappey Consequently a large group of varices radiating outward to join the epigastric veins (caput medusae) may form about the umbilicus Anastomoses also develop through the suspensory ligament between the portal veins of the liver and the veins of the diaphragm emptying into the vena azygos (4) through the veins of Retzius which connect the portal radicles in the intestines and mesentery to the inferior vena cava (retroperitoneal veins)

Changes in other areas are largely the result of the portal obstruction Ascites is usually a marked feature the spleen is enlarged by congestion and possibly as the result of toxemia the gastric and intestinal mucosae are congested and catarrhal and the pancreas often shows chronic interstitial fibrosis

The sequence of events in portal cirrhosis is generally believed to be (*a*) degeneration of the liver cells in the periphery of the lobules caused by poisons carried in the portal vessels (*b*) regenerative hyperplasia of the remaining liver cells and bile ducts with proliferation of the interstitial tissue and contraction (*c*) portal obstruction and the attempt to establish a collateral circulation The increase in fibrous tissue may be partly due to replacement and partly to an inflammatory reaction to the causative toxin

Symptoms—It is by no means uncommon for portal cirrhosis to exist unsuspected during life and only be found after death from accident intercurrent infection or other disease The early recognition of the disease therefore may be extremely difficult and often the first signs are those due to well developed portal obstruction such as hematemesis or ascites Careful investigation however usually reveals evidence of gastric disturbances such as loss of appetite nausea flatulence and occasional vomiting These symptoms may appear periodically Often such symptoms in an alcoholic subject are considered to be the result of alcoholism itself as indeed they may be and the onset of symptoms directly referable to the cirrhosis is frequently overlooked Sooner or later however unmistakable signs usually appear

The congestion of the gastric and intestinal mucosa produces nausea loss of appetite and even vomiting especially in the morning The bowel movements are irregular, the skin sallow, and the conjunctivae muddy Vascular spiders frequently appear on the face arms and upper trunk There is often low grade persistent fever The tongue is often coated and the breath offensive As the obstruction progresses bleeding may take place from the esophageal varices or from hemorrhoids and cause hematemesis and melena the latter often due to blood which has passed from the stomach into the bowel The hematemesis may be the first symptom but usually occurs after obstruction of the portal flow has become quite marked About 25 per cent of patients vomit blood of these approximately one third die from hemorrhage Ascites develops in about 80 per cent of cases and is a prominent feature in the great *majority of those who die of the disease* It is due apparently not only to portal obstruction but also to altered serum proteins and in certain cases to chronic peritonitis Tortuous collateral veins may be seen coursing along the distended abdominal wall and lower thorax The ascitic fluid is yellowish or straw colored with a specific gravity below 1 016 It is usually clear but may be somewhat turbid because of chronic peritonitis or previous tapping The predominating cells are endothelial in type

Peripheral edema likewise occurs commonly in these patients due presumably to changes in the serum proteins In about 80 per cent of patients the liver is palpable and firm and it frequently is tender The spleen is palpably enlarged in about one half the cases Although jaundice is not so conspicu

ous a feature here as in the biliary type of cirrhosis it is present at one or another time in about two thirds of the patients Persistent jaundice indicates activity of the disease process and it should be regarded seriously Hemorrhagic phenomena such as nosebleeds bleeding gums and pupura are not uncommon They probably are related to reduction in the plasma prothrombin

Although toxic symptoms usually develop during the later stages of the disease they may appear at any time If early they are not likely to be severe—depression headache loss of memory, and general malaise being the most common Later, or at any time more marked signs of toxemia such as delirium, drowsiness coma or even convulsions may appear The nature of the toxemia is unknown but is believed by some to result from metabolic disturbances caused by loss of liver function

Laboratory Findings—There is a tendency towards macrocytic anemia which seldom is severe However if chronic blood loss occurs there may be profound hypochromic anemia The white blood cell count is either normal or decreased Leukocytosis generally indicates the presence of some complication With the onset of failure the urine becomes decreased in amount concentrated and contains an excess of urobilinogen The serum bilirubin or icterus index usually shows slight elevations from time to time and rarely shows marked increases The serum proteins may be altered early in the disease Characteristically there is decreased serum albumin and increased serum globulin Whereas the serum globulin values are variable the serum albumin values correlate fairly well with the clinical course That is the serum albumin tends to increase during clinical improvement and to decrease during failure A value below 2 5 Gm per cent is of serious import Plasma prothrombin is reduced in about one half the cases The administration of vitamin K fails to restore normal values for prothrombin in the presence of severe liver damage Indeed this failure to respond to vitamin K therapy has served as a test for impaired liver function The plasma fibrinogen however is usually normal The nonprotein nitrogen is unaltered except terminally when it may rise The serum total cholesterol cholesterol ester and alkaline phosphatase may be normal or moderately reduced

Since the liver has many functions no single test can give an overall index to its competence It is advisable therefore to employ several tests which measure different functions For example the bromsulfalein dye test and bilirubin excretion test are measures of excretory function the urine urobilinogen is a measure of pigment metabolism, the intravenous galactose test is a measure of carbohydrate function The hippuric acid test may or may not be altered in this disease Other tests which depend upon the presence of abnormal serum proteins in cirrhosis have been useful as diagnostic aids These include the cephalin flocculation reaction Takata Ara, and colloidal gold tests Whereas they may occasionally give false positive values it is seldom that these tests are negative in the presence of liver disease

Complications—It is often difficult to distinguish sharply between what may be regarded as less common symptoms and complications The supervention of *acute infection*, such as pneumonia erysipelas peritonitis phlebitis and endocarditis is frequent and serious These infections account for about 25 per cent of the deaths from cirrhosis With the advent of sulfonamide drugs, this danger has been lessened In general the sulfonamides (sulfadiazine) are well tolerated by these patients Whereas active *tuberculosis* was formerly a common complication it has been reported in only 2 or 3 per cent of the cases in recent series

Portal cirrhosis is often complicated by *abdominal hernia* This is due presumably to increased intra abdominal pressure *Peptic ulcer* occurs in possibly 5 to 10 per cent of cases In certain instances of cirrhosis hematemesis has been due to complicating peptic ulcer rather than to the suspected rupture of a varix *Portal thrombosis* occurs rarely It seems to be more frequent in patients who have experienced abdominal surgery It also may be found in those cases of cirrhosis (4 per cent) that develop *primary carcinoma* of the liver

Diagnosis—During the early stages of portal cirrhosis the symptoms are so vague that definite diagnosis is often very difficult

In an alcoholic patient or an individual who has led an irregular life persistent dyspepsia with repeated attacks of biliousness and perhaps slight jaundice should arouse suspicion of early hepatic cirrhosis Added confirmation is given if the liver be enlarged and tender and the spleen enlarged Later the hepatic facies is characteristic, the patient is thin the eyes sunken the nose sharp distended venules appear on the nose and cheeks and the skin is muddy or subicteroid Definite signs of portal obstruction render the diagnosis certain

The ordinary portal cirrhosis can be differentiated from the *syphilitic type* by the absence of a history of infection and a negative reaction to the Wassermann test It must be kept in mind however that syphilis may and often does exist in a patient with nonsyphilitic portal cirrhosis Hematemesis without ascites may suggest *peptic ulcer* In this condition pain has a definite relationship to the taking of food and the liver and spleen are not enlarged Fluoroscopic examination after a barium meal helps to exclude the possibility of ulcer and *malignant disease* of the gastro intestinal tract

Primary carcinoma of the liver may be indistinguishable in its symptoms and signs from portal cirrhosis This is to be anticipated since primary carcinoma generally is superimposed on cirrhosis of the liver If the liver increases rapidly in size or if there is hemoperitoneum the diagnosis of malignancy should be considered *Secondary carcinoma* of the liver usually shows evidence of spread elsewhere Occasionally metastases are confined to the liver In such instances diagnosis is difficult for the clinical picture may simulate cirrhosis closely *Adherent pericardium* with persistent ascites may be mistaken for portal cirrhosis The elevated venous pressure and disturbed cardiodynamics however serve to differentiate this condition clearly from portal cirrhosis

Prognosis—Accurate prognosis is impossible because of the wide variations in the course of the disease At times when there are no major symptoms the disease may remain unrecognized throughout life and the victim die from some other cause Again the disease may be acute and end fatally in a few months The great bulk of cases fall between these extremes and the average duration from the onset of definite evidence of cirrhosis until death is about two years

When signs of liver failure appear such as ascites jaundice and hematemesis the prognosis immediately becomes grave After the onset of ascites about half the patients survive six months and about one third survive one year In the opinion of certain authors jaundice bears a similar prognostic significance in patients with cirrhosis In the case of hematemesis about one third die shortly after the first episode and an additional third die by the end of the first year However recent changes in therapy—notably treatment with dietary measures and the control of intercurrent infections with sulfonamides—may modify considerably the grave outlook previously taken of this disease

Treatment—In the preascitic stage and before hematemesis has occurred the therapeutic measures should rectify the patient s mode of life and personal hygiene When signs of liver failure appear such as ascites or jaundice the patient should be placed at bed rest Alcohol should be prohibited Although anorexia may be present the patient should be urged to eat He should be fed a nutritious high caloric diet of high protein (110–120 Gm) moderate carbohydrate and fat content Meat fish milk eggs fruit and green vegetables should constitute the bulk of the diet A satisfactory regimen includes eggs for breakfast meat at luncheon and supper milk at each of three meals In addition a milk drink containing powdered brewers yeast (15–25 Gm) may be given twice daily between meals If powdered yeast is not tolerated vitamin B complex should be substituted in the form of liquid yeast concentrates Thiamin chloride (5 mg) and unconcentrated liver extract (5 cc) may be injected intramuscularly twice weekly The treatment should be pursued diligently over a period of months According to recent reports upon following the above dietary program a significant number of patients have experienced the loss of ascites and have made considerable clinical improvement

Fluids are allowed up to about 2 liters daily in patients with ascites Salt should be restricted to the amount ordinarily used in the kitchen in preparing the food Ab

dominal taps should be done before distention interferes seriously with the patient's appetite In order to lengthen the intervals between paracenteses, mercurial diuretics may be injected once or twice weekly together with ammonium chloride by mouth If the prothrombin is low vitamin K should be administered, and if hypochromic anemia is present ferrous sulfate may be given

For hematemesis the patient should be kept absolutely quiet in bed and all food omitted for two or three days An ice bag should be placed over the epigastrium, and if the patient is restless, morphine given hypodermically in small amounts If hemorrhage is severe transfusion of fresh citrated blood should be given early and if signs of hemorrhage persist the transfusion should be repeated Vitamin K concentrates may be given parenterally Hypodermoclyses of normal saline should be given if the patient is dehydrated Semiliquid and later soft diets may then be instituted

In the past surgical procedures such as omentopexy and splenectomy have been advocated for the treatment of portal cirrhosis The consensus of opinion at present is that the results obtained do not justify the risks involved in these operations

Biliary Cirrhosis —Two forms of biliary cirrhosis are recognized the primary (Hanot), and the secondary or obstructive (Charcot)

Primary Biliary Cirrhosis (*Hypertrophic Biliary Cirrhosis Infective Biliary Cirrhosis Hanot s Cirrhosis*) —Definition —Primary biliary cirrhosis is a chronic disease of the liver characterized clinically by persistent jaundice with enlargement of the spleen and liver and anatomically by a catarrhal inflammation of the small bile ducts and intralobular fibrosis

Etiology and Pathogenesis —It is a rare disease which occurs in youth and early adult life Males are more often affected than females Boyd points out that the condition is not an entity but includes two or three conditions the most important of which is infective He suggests that the name Hanot be dropped Although the disease is said to be familial or even hereditary in certain cases a definite distinction has not always been clearly made between Hanot s cirrhosis and hemolytic (familial) jaundice The immediate cause is unknown Primary biliary cirrhosis has in a number of instances, definitely followed an infection, such as typhoid fever This fact and the clinical picture have led most observers to regard infection as the most probable cause of Hanot s cirrhosis The usual absence of evidence of infection in the duodenum and larger bile ducts renders the possibility of an ascending infection unlikely, and Rolleston inclines to the view that the infection (or toxin) reaches the small bile ducts through the hepatic artery The fibrotic changes are believed to be secondary to the cholangitis

Morbid Anatomy —The liver is uniformly enlarged sometimes weighing 3800 Gm The surface is smooth or finely granular dark green in color, and may show some perihepatic adhesions The organ is firm in consistency, cuts with resistance, and presents a uniform granite like yellowish green appearance Microscopically a dense fibrosis can be seen to surround the individual lobules and small bile ducts It may actually extend into the lobule (intralobular fibrosis) The liver cells themselves do not undergo any marked change and the larger bile ducts are likewise comparatively unaffected

In the portal areas the smaller bile ducts show evidence of catarrh and proliferation and in many cases contain dark staining columns of cells, the so-called *pseudobile canaliculi* These structures are formed in an attempt at regeneration, a reactive hyperplasia of the cells of the bile ducts

When the disease is advanced the picture may be confused by the development of multilobular cirrhosis Indeed it is often very difficult to classify certain borderline cases from a histologic standpoint

The spleen is enlarged and shows endothelial proliferation and fibrosis The periportal lymph nodes are enlarged and often all the glands All the organs are stained with bile

Symptoms —The *onset* which is insidious is sometimes manifested by vague gastro intestinal symptoms such as mild dyspepsia pain vomiting and diarrhea Often the first definite symptom is jaundice, but this may be preceded by pruritus The jaundice is usually slight but persistent it may vary in degree from time to time The

urine and feces contain bile The liver is found to be enlarged and may be tender The *spleen* is palpable Periodic attacks of mild fever abdominal pain leukocytosis and progressive hepatic and splenic enlarge ment and tenderness may occur There is no evidence of portal obstruction unless multi lobular fibrosis supervenes in the advanced stage

The *course of the disease* is chronic the symptoms gradually becoming more pro nounced and the general nutrition of the pa tient failing as time elapses Three to six years is a common duration Death results from an acute degeneration of the liver cells resembling acute yellow atrophy or from profound cachexia In the later stages hem orrhages into the skin and from the mucous membranes may occur Clubbed fingers have been noted

Diagnosis —The insidious onset in young persons of a mild but persistent jaundice gastro intestinal disturbance enlargement of liver and spleen and periods of slight fever leukocytosis and abdominal pain should suggest hypertrophic biliary cirrhosis The condition must be differentiated from *portal cirrhosis* (age signs of portal obstruc tion history of alcoholism) from *cholelith iasis or other types of obstructive jaundice* (history deep jaundice clay colored stools slight enlargement of liver and spleen) and from *hemolytic jaundice* (acholuric urine increased fragility of red cells)

Treatment —The disease cannot be defi nitely arrested The general health should be maintained in so far as possible by care ful avoidance of exposure to cold and wet a generous but simple diet and plenty of sun light and fresh air The pruritus may be relieved by measures already recommended for that of other types of jaundice Admin istration of calomel (grain 1/8 3 times a day for several days) has been recommended Drainage of the gallbladder and bile ducts gives good results in certain cases but has not come to be a routine method of treat ment Lyon s method of nonsurgical drain age of the gallbladder and bile ducts by the duodenal tube may produce equally good results without incurring danger W J Mayo has reported that splenectomy was a successful form of treatment in three cases

Obstructive Biliary Cirrhosis (*Secondary Biliary Cirrhosis Charcot s Cirrhosis*) — Obstructive biliary cirrhosis results from the proliferative fibrosis brought on by chronic obstruction of the larger bile ducts by gall stones new growths or adhesions As the name implies the fibrosis extends out from the intrahepatic bile ducts and produces a condition not unlike that of Hanot s cirrho sis except for the less marked enlargement of the liver A cholangitis involving the larger bile ducts is also present The gall bladder may or may not be distended according to the nature of the obstruction (see *Courvoisier s Law*)

Symptoms —The symptoms are those of the cause of the obstruction and those of chronic obstructive jaundice The liver is defi nitely enlarged and firm Recurring attacks of chills and fever (Charcot s intermittent hepatic fever) are common The spleen is not uniformly palpable as in Hanot s disease

Treatment —The treatment is that of the cause of the obstruction and is usually surgical

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ABSCESS OF THE LIVER

(*Suppurative Hepatitis Purulent Hepatitis*)

Etiology —Suppurative hepatitis or ab scess of the liver is always due to infection The organism may be carried to the liver by

either the portal or hepatic blood stream, by the bile passages after suppurative cholangitis by direct extension from neighboring infection and from external sources by traumatism

The commonest type is that in which multiple abscesses develop as a result of infection by emboli from foci in the area drained by the portal vein or as a manifestation of a general pyemia in which the infective agent reaches the liver through the hepatic artery Rarely the infection has been known to be carried in the hepatic veins (retrograde emboli) In the portal area the emboli arise from ulcerative disease of the gastro intestinal tract from acute appendicitis rectal and pelvic infections and following rectal or low abdominal operations for herniae hemorrhoids and others In such cases as Osler points out the abscesses are as a rule within the branches of the portal vein (suppurative pylephlebitis) If infection takes place by way of the hepatic artery it is secondary to such conditions as ulcerative endocarditis septicemia and pyemia

Tropical abscess (*solitary abscess*) is usually single and is caused almost always by infection with the *Entamoeba histolytica* As its name implies the disease occurs most commonly in tropical climates It is ordinarily the result of previous amebic dysentery but may develop without infection of the bowel Overindulgence in alcohol and overeating are said to be predisposing factors The incidence is higher among the foreign population in India than among the natives The route by which the organism reaches the liver is not definitely known but the general weight of opinion is that it travels by way of the portal vein Amebic abscesses may form many years after an attack of dysentery

Suppurative cholangitis is not an uncommon precursor of hepatic abscess The infection spreads by extension along the bile ducts into the liver substance Direct extension may also occur from an infected gall bladder from subphrenic abscess or other suppurative lesion in the vicinity of the liver

Traumatism is not a frequent cause of abscess of the liver It may occur as a result of accidental injury or of a stab wound in which the bacteria are introduced directly from without The causative wound need not be perforating as injury to the liver from indirect contusion or laceration may cause the localization of blood borne organisms which come from infections elsewhere in the body

The ordinary pyogenic organisms such as *Streptococcus Staphylococcus Pneumococcus Bacillus coli* are those usually present in the abscess Occasionally *Bacillus typhosus* or *Bacillus dysenteriae* may be found The tubercle bacillus and the ray fungus (*Actinomyces*) are rarely encountered

Hydatid cysts in the liver may become infected with pyogenic bacteria and cause an abscess Rarely the presence of round worms and flukes in the liver causes a purulent hepatitis

Morbid Anatomy—The tropical or amebic abscess is usually single and, in about 75 per cent of cases situated in the right lobe The abscess may be very large and contain a surprising amount of material As much as 8 quarts of fluid have been taken from a single abscess Externally there may be perihepatic adhesions especially to the diaphragm The abscess cavity is lined at first with rough necrotic tissue but later the walls become smoother as fibrous tissue surrounds the abscess and invades the neighboring parts of the liver The contents of the abscess are usually reddish brown in color glairy in consistency and under the microscope can be seen to contain broken down liver and blood cells and *Entamoeba histolytica* Leukocytic infiltration of the wall is not the rule An amebic abscess is therefore really an area in which necrosis and digestion of the tissue have occurred rather than a true abscess In a certain number which become secondarily infected with pyogenic organisms creamy pus is present Sometimes the amebae can be found in the wall of the abscess when examination of the contents fails to reveal them

Solitary abscesses of the liver are also occasionally caused by bacterial infection particularly in cases of traumatism

Pyemic abscesses and those secondary to suppurative cholangitis are usually multiple The former type may be miliary and are distributed along the course of the blood vessels while the latter extend into the liver substance from foci in the bile ducts Fre-

quently multiple abscesses coalesce so that the whole area involved assumes a spongy appearance because of the uneven areas of necrosis and liquefaction

The contents of the nonamebic abscesses are definitely purulent and contain many pus cells as well as detritus from broken down tissue

In suppurative pylephlebitis the infection originates in the area drained by the portal vein (appendiceal abscess ischiorectal abscess) and sets up first a portal periphlebitis The inflammation extends inward involving the intima and resulting in thrombosis The thrombus becomes infected softens and in breaking down forms pus The process may be extended to the liver by direct continuity or by infected emboli from the suppurating area The liver is uniformly enlarged and its entire portal area may be involved in the suppuration The abscesses may be separate and produce a honeycombed appearance or may coalesce

Symptoms —*Solitary Abscess* —Often a solitary hepatic abscess produces no special symptoms and may be unsuspected during life (latent abscess) Usually however a fairly definite syndrome permits correct diagnosis In amebic infections the symptoms may develop during or after an acute attack of dysentery The onset may be sudden but is often insidious Malaise intermittent fever chills pain in the right upper quadrant with enlargement and tenderness of the liver leukocytosis and slight jaundice are commonly present The chills and intermittent fever often suggest malaria Profuse sweating is common The pain is variable often radiates to the right shoulder or scapular region and if the abscess approaches the surface may be sharp and stabbing in character It is aggravated by deep breathing and palpation With perihepatitis a friction sound may be heard over the liver As a rule the patient is most comfortable when lying on the right side or back turning to the left side often produces a dull aching or dragging sensation in the right hypochondrium Loss of appetite weakness emaciation and a septic appearance are usually present and progressive

When the abscess is deeply situated the enlargement of the liver may be slight at first and there may be no change in the contour of the organ Later when the abscess has attained a large size or when it is situated anteriorly and toward the lower margin the enlargement is easily demonstrable and a bulging of the right side of the abdomen may be detected If the abscess is close to the diaphragmatic surface of the right lobe an upward displacement of the right lung is evident on percussion and can be seen in x ray plates Abdominal breathing is restricted

Jaundice develops in only 15 per cent of patients and is not marked A pale muddy or sallow appearance of the skin with subicteric tinting of the sclera is however usual Nausea and vomiting may occur and intestinal irregularities (diarrhea constipation) are common

Ascites is rare and the spleen is seldom enlarged

Pyemic Abscess and Suppurative Pylephlebitis —The symptoms of pyemic abscess and suppurative pylephlebitis are masked to a large extent by those of the primary disease The clinical picture is that of general septicemia or localized septic infection such as appendiceal abscess pyonephrosis lung abscess or other infection likely to give rise to pyemia Chills sweats remittent fever with malaise vomiting weakness wasting slight icteroid tinging of the skin and conjunctivae and tenderness over the liver are suggestive There are however no signs pathognomonic of involvement of the liver and usually the multiple abscesses are but one manifestation of the original infection There is usually a pronounced leukocytosis (polymorphonuclear) in this type of hepatic abscess

Complications —The abscess may rupture if not operated on This occurs not infrequently and the rupture takes place most often through the diaphragm and pleural sac into the lung A lung abscess is thus produced which may in turn rupture into a bronchus If the infection be amebic the sputum is then brownish (anchovy colored) and contains shreds of liver tissue and amebae Rupture may also occur into the bowel into the peritoneal sac and rarely into the pericardium Secondary abscesses in the lungs are not uncommon

Diagnosis of abscess of the liver is often difficult A history of dysentery the devel

opment of a clinical picture of sepsis (chills sweats irregular fever), and signs of hepatic involvement (enlargement tenderness pain in hepatic region) constitute the most significant signs in the amebic cases X-ray examination may be valuable In pyemic abscesses the clinical picture is that of pyemia or septicemia and often there is little evidence of involvement of the liver although enlargement pain and tenderness over the liver may suggest the correct diagnosis

In malarial regions the condition must be differentiated from *malaria* Examination of the blood for the malarial parasite the leukocyte count and the therapeutic test with quinine suffice for this Liver abscess may be distinguished from *suppurative cholangitis* by the occurrence in the latter of earlier and more pronounced jaundice and a frequent history of cholelithiasis In 'intermittent hepatic fever associated with *gall stones* the differential features are the paroxysms of pain chills sweats followed by deepening jaundice with afebrile and (usually) apparently normal intervals If the hepatic abscess is large and located in the upper part of the liver the diaphragm may be high and the lung compressed Such a condition may suggest *empyema* but the history the limits of dulness on percussion and the x ray findings usually suffice for differentiation Diagnostic puncture of the liver may be employed if the presence of a solitary abscess is suspected but involves some risk of hemorrhage and peritonitis Blood examinations (cultures counts parasites Wassermann test) should prevent confusion with *syphilis of the liver trypanosomiasis typhoid fever leukemia* and *malignant endocarditis* The history complement fixation test and exploratory puncture sometimes permit diagnosis of a suppurating *echinococcus cyst* in the liver

Prognosis—Multiple abscesses of the liver are practically always fatal whether they be due to suppurative pylephlebitis pyemia or extension from suppurative cholangitis Solitary abscesses on the other hand may not prove fatal when rupture takes place into the bowel or even into the lung or when surgical evacuation is successful If the abscess remains intact death usually results from toxemia or pyemia

Treatment—The treatment of *solitary abscesses* due to pyogenic infection is surgical together with sulfonamide therapy appropriate to the type of bacterium involved. Evacuation and drainage of the abscess should be performed as soon as the diagnosis is made If the infection is amebic emetine 1 grain hypodermically for six successive days, ½ grain for four successive days, should be given as well Repeated aspiration of single abscesses has been recommended by some observers as preferable to open drainage Surgical drainage of amebic abscesses has few remaining advocates

General therapy consists of absolute rest in bed, light diet application of poultices or compresses to the hepatic region and regulation of the bowels During convalescence, open air nourishing food and tonics are advisable

The treatment of *pyemic abscesses* and *suppurative pylephlebitis* is largely symptomatic and palliative since these conditions are almost invariably fatal Cases have recently been reported however in which recovery has taken place after sulfanilamide therapy

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MALIGNANT DISEASE OF THE LIVER

Under the heading of malignant disease of the liver carcinoma and sarcoma of the liver both primary and secondary will be considered

Incidence and Etiology—*Primary carcinoma* of the liver is rare but is seen more often than primary sarcoma of the liver It is more common in males than females and occurs in individuals about fifty years of age There is however a wide range as far as age is concerned The writer recently ob

served a case in a young woman of twenty one *Secondary carcinoma* of the liver is very common and develops in about 50 per cent of all the victims of malignant disease The primary growth responsible for the sec ondary metastases in the liver is most com monly found in the stomach but frequently occurs in other parts of the digestive tract especially in the colon Not infrequently the primary lesion is in the breast the eye the pancreas the gallbladder or the genito urinary tract (prostate uterus and so on) Females are slightly more susceptible than males (four to three) probably because of the frequency of cancer of the uterus The patients are usually more than forty years of age

Primary sarcoma of the liver is extremely rare *Secondary sarcoma* constitutes nearly 10 per cent of malignant disease of the liver and is most frequently due to metastases from primary growths in bones adrenals mediastinum the eye and the skin The age incidence is that of sarcoma in general and is therefore lower than that of carcinoma

Morbid Anatomy.—Eggel divides *primary carcinoma* of the liver into three types (1) the nodular and common form in which there are scattered tumors throughout the organ (2) the massive form in which a single large neoplasm is found often with small metastatic nodules in its vicinity and (3) the diffuse form in which the whole liver is infiltrated with small cancerous nodules surrounded with marked connective tissue hyperplasia This latter type gives rise to a gross picture very like that of cirrhosis of the liver which can often be recognized as malignant only on microscopic examina tion Rolleston believes that the cirrhosis is primary and that the carcinoma is the out come of hyperplasia of the hepatic cells

Secondary carcinoma appears as multiple grayish white nodules of varying size and number which when superficial often cause the surface of the liver to bulge and form definite bosses which may be umbilicated Frequently these bosses are palpable through a thin abdominal wall The liver as a whole may be enormously enlarged Christian re- ports that in one case it weighed 33½ pounds The nodules on section often show central areas of degeneration and hemor rhage so that the original firm consistency is lost The shrinkage of the necrotic center and the contraction of the fibrous tissue pro duce the umbilication mentioned above Microscopically the tumor presents the char acteristics of the primary lesion and is most commonly alveolar or columnar in structure

Primary sarcoma of the liver is usually a massive growth The tumor is often hemor rhagic and may break down in the center to form pseudocysts In another form there are multiple nodules and occasionally a third type is seen which shows diffuse infil tration resembling that in the liver in con genital syphilis Secondary sarcoma may be of the melanotic type the primary lesion being in the eye or less commonly in the skin Less important types are lymphosar coma and myxosarcoma

Symptoms.—The onset is very insidious and is manifested by weakness loss of ap- petite and failure in general health As in the case of malignant disease elsewhere there is usually progressive loss of weight and increasing secondary anemia

Symptoms indicative of involvement of the liver itself may arise at any time These are usually discomfort or pain in the right hypochondrium jaundice and ascites It is often impossible to distinguish primary malignant disease of the liver from the sec- ondary type unless there is evidence of a primary growth elsewhere

The enlargement of the liver is usually progressive Often the irregular bulging of the right hypochondrium can be seen through a thin abdominal wall and on palpation the bosses with their umbilicated centers may be felt In such cases the diagnosis is certain In other patients however the liver is not enlarged and definite diagnosis is im possible Jaundice which is apparent in about 50 per cent of cases is usually due to pressure of a cancerous nodule upon the intrahepatic bile ducts but may be caused by the pressure of enlarged glands on the larger ducts Ascites is common but is not seen as frequently as jaundice It may be due to pressure upon the portal vein by tumor nodules to an associated hepatic cirrhosis to perihepatitis or to extension of the growth to the peritoneum The spleen is usually not enlarged

Irregular fever is a common symptom which may be caused by the cancer itself

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neath the capsule Rarely, they enlarge during adult life and produce clinical signs such as bulging of the abdomen ascites or other symptoms of pressure Solitary and multiple *adenomata* may occur The latter type which is found in some cases of portal cirrhosis is regarded by some as merely an excessive hyperplasia of the liver tissue It is difficult to draw the line between hyperplastic areas and adenomata and between adenomata and carcinomatous nodules Some pathologists consider the adenoma a transitional stage between hyperplasia and malignancy

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CYSTS OF THE LIVER

Simple cysts are usually small and single They are commonly attributed to local obstruction of the bile ducts either congenital or associated with inflammatory change They have no clinical significance

Cystic disease of the liver is a rare condition usually associated with congenital cystic kidneys The cysts are usually small multiple and filled with a clear serous fluid The condition is probably congenital although it is seldom recognized until adult life and then only if the kidneys are affected

Echinococcus cysts are discussed elsewhere

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DEGENERATIVE DISEASES OF THE LIVER

Fatty Liver—It has been the custom to consider fatty lesions of the liver as of two types—infiltrative and degenerative The former type has been thought to be a condition in which fat derived from the usual fat deposits in other parts of the body is deposited in the liver after transportation by way of the blood stream without any actual damage to the liver cells whereas the latter type has been thought to be a primary degeneration of the protoplasm of the liver cells into fat This distinction is not as sharp as such classification would imply since in certain conditions such as phosphorus poisoning in which the lesion is usually regarded as degenerative some of the fat in the liver is derived from other parts of the body Clinically however the degenerative types form a rather definite group including phosphorus arsenic alcohol and chloroform poisoning acute yellow atrophy and occasionally acute infections The infiltrative type is commonly found in (*a*) obesity (*b*) conditions supposed to reduce the oxidative powers of the body such as anemia cachexia and pulmonary tuberculosis and (*c*) infections such as septicemia typhoid fever, and the acute exanthemata

Morbid Anatomy—The fatty liver is usually uniformly enlarged smooth with rounded edges and pale It is greasy on section and as a rule appears rather bloodless In cases associated with passive congestion however it may present the characteristic nutmeg appearance Microscopic examination reveals in the liver cells fat droplets usually of large size which press the protoplasm and nucleus aside The most marked change is toward the periphery of the lobule In the degenerative types the liver may be smaller than normal This reduction in size is often extreme in acute yellow atrophy The fat droplets are usually minute and the cell nucleus and the cytoplasm show evidence of degeneration In many cases of fatty liver both types of change are simultaneously present

Symptoms—The clinical picture is mainly that of the associated disease Symptoms referable to the liver itself may be absent but a sense of fulness and discomfort in the hepatic region is often noted Jaundice ascites and pain are absent in the simple cases Vague gastro intestinal disturbances may occur

Diagnosis—The association of one of the causative conditions cited above with the presence of an enlarged smooth soft and painless liver without jaundice should suggest fatty change In obese subjects it may be difficult to determine the size of the organ The history the associated conditions examination of the spleen and the blood findings help to differentiate fatty liver

or by suppuration in a degenerating cancerous nodule The blood examination reveals a secondary anemia and frequently a moderate leukocytosis The urine contains bile pigment when the jaundice is deep A positive Wassermann reaction in the blood without other evidence of syphilis has been reported In one such case in the writer's experience the reaction was persistent but antisyphilitic treatment had no effect on the progress of the disease It is probable that the latent syphilis had no relation to the neoplasm

Diagnosis —An insidious onset with progressive nodular enlargement of the liver anemia and loss of weight and strength in a person at or past middle age are characteristic signs The diagnosis is conclusive if a primary malignant growth elsewhere be demonstrable The presence of jaundice and ascites is additional evidence Aspiration biopsy is a justifiable procedure in doubtful cases

It is often impossible in the absence of signs of a primary lesion to distinguish between primary and secondary malignancy of the liver The primary focus may be latent

Syphilis of the liver may be recognized by the history of infection the evidence of luetic lesions elsewhere in the body the blood examination and the therapeutic test As pointed out above the possibility of the coexistence of these diseases must be kept in mind An *echinococcus cyst of the liver* may simulate cancer but the history the softer consistency of the tumor the presence of hydatid thrill and the slower development without marked cachexia are differential points *Hepatic abscess* presents signs more characteristic of infection namely rigors and fever marked leukocytosis and sweats A history of amebiasis or a pyemic condition is common jaundice or ascites on the other hand are evidences of cancer *Portal cirrhosis* in its earlier stages may cause enlargement of the liver but the enlargement is more uniform on palpation there are evidences of portal obstruction with enlargement of the spleen the disease progresses slowly and the liver tends to decrease in size *Biliary cirrhosis* occurs in younger individuals the enlarged liver is smooth the spleen is enlarged the jaundice early and the course very chronic *Obstruction of the common bile duct with gallstone* causes changes resembling those of malignancy such as jaundice and enlargement of the liver with local pain and tenderness The enlargement however is usually slight, while the pain is paroxysmal and associated with chills and fever The jaundice tends to fluctuate and there is usually an antecedent history pointing to cholecystitis

Prognosis —As a rule malignant disease of the liver terminates fatally within from three to twelve months after enlargement of the liver has been noted The course of the primary is usually more rapid than that of the secondary type

Treatment is chiefly palliative Relief of pain is secured only by the use of morphine. This should be given in doses sufficient to keep the patient comfortable If the liver is very large a binder or supporting belt may be advantageously employed The appetite is improved to some extent by the ingestion of dilute hydrochloric acid (1 drachm with meals) and vomiting may be combated by the administration of bismuth dilute hydrocyanic acid or morphine The bowels should be regulated by salines For the itching calcium lactate 1 Gm (15 grains) three times daily may be given internally, and carbolic acid (1 60) or soda bicarbonate solution externally The hypodermic administration of atropine pilocarpine or morphine is sometimes helpful in obstinate cases Operation for removal of the tumor is rarely possible but when the growth is solitary such treatment may be justifiable

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BENIGN TUMORS OF THE LIVER

Benign tumors of the liver are uncommon and are of little clinical importance *Hemangiomata* which are occasionally seen are as a rule small and situated just be-

Jaundice is often the outstanding sign of disease of the biliary tract The jaundice which is associated with abnormalities of the bile ducts is of the regurgitation type As Rich has pointed out regurgitation jaundice includes those cases in which bile gains access to the blood This group is characterized by a prompt van den Bergh reaction and the presence of bilirubin in the urine in contrast with retention jaundice in which bilirubin alone accumulates in the blood due to faulty excretion by the liver cells In the latter group which includes hemolytic jaundice and certain milder forms of liver damage the van den Bergh reaction is delayed or indirect and bilirubinuria is absent Regurgitation jaundice is often accompanied by varying degrees of pruritus while retention jaundice is not It may be emphasized that the two forms often occur simultaneously As an example cases of hemolytic jaundice complicated by common duct calculi may be cited The regurgitation jaundice resulting from stone cancer or stricture of the common bile duct is due to increased intrabiliary pressure So far as can be determined this results in rupture of many of the smallest bile ducts within the liver Bloom and others have shown that the bile escapes chiefly into the adjacent lymphatic spaces thence to the thoracic duct and circulating blood There is much experimental work which indicates that regurgitation of bile may also occur as a result of increased permeability of the small bile ducts particularly the ampullary portions of the bile capillaries This change in permeability is caused by a variety of poisons and toxins The jaundice which results may be spoken of as parenchymal in contradistinction to cancerous and calculous jaundice The term cancerous jaundice applies chiefly to biliary tract cancer (involvement of the main bile ducts) There are in addition certain forms of jaundice which are not readily classified with these three main groups such as common duct stricture pressure of benign tumors or cysts Hodgkin s disease or leukemia and parasitic disease All of the latter as well as the various types of parenchymal jaundice are classified from a fundamental standpoint as members of the regurgitation jaundice group but from the standpoint of prognosis and treatment particularly the question of surgery, it is essential that parenchymal jaundice be distinguished from that due to common duct stone cancer of the bile ducts and other extrahepatic biliary tract disease This distinction is at times exceedingly difficult, and may depend upon correlation of data gained in a number of different ways including microscopic study of bile obtained by duodenal drainage (Lyon) study of the degree of biliary obstruction as determined by urobilinogen excretion (Watson) and investigation of liver function by various methods such as determination of the urine urobilinogen galactose tolerance serum proteins cholesterol hippuric acid test and others Cholecystography as devised by Graham and Cole is often of decisive importance in cases without jaundice while in patients with considerable jaundice the procedure is of little or no value and is not recommended

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CHOLELITHIASIS

(*Gallstones Biliary Calculus*)

Etiology and Occurrence—The majority of human gallstones are composed chiefly of cholesterol The concentration of cholesterol in the bile as well as its stability of solution is therefore of much significance Several important factors may be mentioned

Concentration of Bile—The bile is concentrated from five to ten times in the gall bladder and the degree of concentration is increased when the rate of emptying is relatively slow During pregnancy for example gallbladder function is distinctly sluggish (Boyden) with the result that stasis and further bile concentration are favored

from *cirrhosis passive congestion leukemic infiltration amyloid disease* and *displacements*

Treatment —The treatment is that of the primary or causative condition

Amyloid Liver (*Waxy or Lardaceous Liver*) —Amyloid disease of the liver is not common in the United States and Canada It occurs as part of a general degeneration, which is usually most marked in the spleen and kidneys The disease most often attacks young people, usually as the result of long continued tuberculous or other suppuration or of syphilis Occasionally it follows such wasting diseases as cancer anemia, chronic arthritis, and other chronic infections In syphilitic cases there is often tertiary ulceration, but amyloid disease may occur without suppuration The view that it is of toxic origin is supported by suggestive results of experiments in which animals were injected with products of pyogenic bacteria or other toxic substances Probably modern methods of treatment, by reducing the incidence of prolonged suppuration are responsible for the relative infrequence of amyloid disease at the present time

Morbid Anatomy —The amyloid liver is uniformly enlarged and in some cases attains four or five times its original size It is smooth firm and cuts with resistance The cut surface is pale and semitranslucent Stained with Lugol s solution the tissue appears rich mahogany brown in the amyloid areas The median portions of the lobules are affected first the process spreading both centrally and peripherally as the disease advances Microscopically it can be seen that homogeneous amyloid material is deposited in the capillary walls external to the endothelial lining In more advanced cases there is also a deposit about the small branches of the hepatic artery

Symptoms —On clinical examination the liver is found to be uniformly enlarged and smooth but there is no pain or tenderness The patient complains of no symptoms directly referable to the liver unless the enlargement is so great as to cause discomfort in the hepatic area Symptoms of the primary or associated disease are usually present however and include general debility wasting and a pale cachectic appearance The spleen is nearly always enlarged and firm, but there is no ascites Jaundice does not occur

Diagnosis —The history of antecedent or associated disease of a nature likely to caus amyloidosis, and the finding of an enlarged smooth firm, and painless liver and spleen should suggest the diagnosis In the presence of such findings, a positive Congo red test would strongly support the diagnosis The condition must be differentiated from *fatty liver cirrhosis passive congestion leukemic infiltration and displacement*

Treatment —The treatment is that of the disease giving rise to the amyloid change There are no remedies specific for the hepatic lesion The development of amyloidosis of the liver does not affect the prognosis of the case except that to some degree it is an index of the extent of the general disease

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DISEASES OF THE GALLBLADDER AND BILE DUCTS

INTRODUCTION

The central point of interest in this group of diseases is cholelithiasis Gallstones are the most frequent source of symptoms referable to the biliary tract They are commonly related to the development of a variety of abnormalities such as cholangitis, liver abscesses jaundice and biliary cirrhosis Furthermore they are of undoubted significance in the etiology of primary cancer of the gallbladder and ducts The early recognition of gallstones is therefore a matter of considerable importance Modern methods including cholecystography and microscopic examination of bile obtained by duodenal drainage have aided greatly in the diagnosis The history and physical examination however remain indispensable and often sufficient in themselves to suggest strongly the presence of cholelithiasis

which no symptoms had been noted during life This fact makes it difficult to establish the time of formation of gallstones and impossible therefore to correlate them with age in any exact way

Sex—From 5 to 10 per cent of adults of both sexes are found to have gallstones at autopsy Chiefly because of pregnancy perhaps also because of dietary factors obesity and sedentary habits the percentage is much higher among women than men and is probably in the neighborhood of 20 per cent of women who have borne children

Diet—No definite relationship is known although it is true that gallstones are somewhat more common in obese individuals It may be true that overeating particularly of fats is important to the genesis of gallstones because of hypercholesterolemia The relatively rare occurrence of gallstones among Oriental people suggests that differences in diet may be of considerable importance

Variety and Character of Biliary Calculi—Numerous classifications of gallstones have been suggested of which the simplest and most useful especially from a clinical standpoint appears to be that which depends on whether the stone is relatively pure in composition or a distinct mixture of two or more substances On this basis gallstones may be subdivided as follows (1) Pure stones either cholesterol calcium bilirubinate or calcium carbonate (2) Mixed stones including a preponderance of cholesterol together with one or more of the other materials just referred to as well as albuminate cellular debris and occasionally foreign bodies such as fragments of worms. Bacteria especially viable typhoid bacilli, may be included (such individuals are not



Fig 79—Cholesterol stones in gallbladder partially filled with dye Arrow indicates so-called phrygian cap (Courtesy of Dr Leo G Rigler)



Fig 80—*a* Solitary cholesterol stone in dye-filled gallbladder *b* Displacement of stone into neck of gall bladder after contraction due to fatty meal (Courtesy of Dr Leo G Rigler)

Cholesterol Content of the Bile—Hypercholesterolemia has been shown to be associated with an increased quantity of cholesterol in the bile During the latter months of pregnancy and for a time after delivery, hypercholesterolemia is marked This, together with biliary stasis as mentioned above is probably important to the definite correlation that is known to exist between pregnancy and gallstone formation Hypercholesterolemia alone cannot be said to produce gallstones since there are a number of diseases, such as myxedema and nephrosis exhibiting hypercholesterolemia, but in which cholelithiasis is no more common than in the normal population Cholesterol is maintained in solution in the bile at least in part, because of the presence of bile salts It is probable that significant reduction in bile salt concentration tends toward precipitation of cholesterol The concentration of bile salts and cholesterol in the bile depends in part on the normal function of the liver cells In conditions associated with hepatocellular damage the concentration of both the bile salts and cholesterol tends to diminish This may explain the fact that gallstone formation has not been correlated definitely with parenchymal liver disease such as due to various poisons and infections Nevertheless since gallstones may be present for long periods without manifestations it is impossible to be certain that some previous toxic effect on the liver was not responsible for the onset of stone formation due to a temporary lowering of bile salt concentration in the bile There undoubtedly are instances of liver damage in which the bile salt concentration is relatively much lower than that of cholesterol

Infection—Naunyn believed that infection preceded all gallstones He pointed out that stasis is usually preliminary to infection The importance of infection to gallstone formation is as follows (1) the fact that small masses of exudate (leukocytes fibrin epithelial cells) serve as nuclei around which precipitation of cholesterol and other substances takes place Precipitated albumin favors the precipitation of calcium bilirubinate either in crystalline or amorphous state Infection is probably the chief factor in the formation of multiple gallstones in contradistinction to the solitary, large cholesterol stones which are usually regarded as metabolic and noninfectious in origin According to Aschoff the latter commence with the precipitation of cholesterol on some one occasion and any subsequent precipitation results simply in an increase around the solitary nucleus After infection however, there are multiple nuclei about which subsequent precipitation may take place. The equal growth around multiple nuclei accounts for the fact that the gallstones in any one gallbladder are commonly of the same general size (2) Infection alters the bile salt cholesterol ratio in the bile So far as can be determined at present this is due to two factors Infection probably accelerates bile salt reabsorption from the mucosa of the gallbladder Infection tends to decrease the bile salt concentration because of suppression of liver cell activity Whether infection has any influence on cholesterol concentration is unknown Chauffard believed that the frequency of gallstones after typhoid fever was related to hypercholesterolemia It appears however that biliary stasis, toxic suppression of bile salt formation and multiple exudative nuclei are equally, or even more important factors Gallstones from patients who have had typhoid fever not uncommonly contain viable typhoid bacilli

Bilirubin Concentration—In conditions associated with a marked and prolonged increase in the amount of bilirubin excreted in the bile such as hemolytic jaundice and pernicious anemia there is a distinct tendency for bilirubin to precipitate as the calcium compound

Calcium Carbonate—Phemister has emphasized the fact that obstruction of the cystic duct by one of the common variety of stones or by carcinoma may be followed by precipitation of calcium carbonate either in the form of a stone a cast of the gall bladder or a soft milky suspension

Predisposing Factors—*Age*—Clinical manifestations of gallstones are observed much more commonly after the age of forty although they are frequently encountered in younger women who have had one or more pregnancies While it is probable that gall stones usually produce symptoms within a few months after their formation there are many instances encountered at autopsy in

ance of persistent jaundice Chills and high fever may not be observed in these cases although a low grade temperature elevation is not uncommon

Physical examination reveals an enlarged liver firm and finely roughened particularly if the jaundice is of long duration At the operation this is found to represent a mild degree of cirrhosis of biliary or obstructive type The spleen is palpable with considerable frequency but not markedly enlarged Ascites occurs rarely Esophageal varices and hematemesis have been noted occasionally, but in such instances the question arises as to whether the cirrhosis was not coincidental and primary rather than secondary to calculous biliary obstruction Biliary or obstructive cirrhosis is undoubtedly related not only to chronic biliary obstruction but perhaps more closely to biliary tract infection associated with calculi Graham has noted the association of cirrhosis with gallstones and biliary infection in individuals who had not been jaundiced

Gallstone Colic (Biliary Colic Hepatic Colic) —Attacks are usually abrupt in onset often commencing several hours after a heavy meal and as a consequence most often occurring in the evening or during the night The colic is due to smooth muscle spasm or stretching of either he gallbladder or ducts The stone may be in the cystic or common duct and the onset of colic follows shortly upon migration of the stone to a new location either from the gallbladder to the cystic or common bile duct or from the dilated common duct into the ampulla The intensity of the colicky pain is variable in different attacks and depends in some degree upon the patient s sensitivity to pain In general the attacks are of a severe nature causing the patient to writhe roll or double up to walk about in anguish to press his fists into his abdomen or to shout or cry because of acute distress In many cases these symptoms are accompanied by profound sweating The pain is located in the right upper quadrant of the abdomen at times somewhat near the midline From the site of onset it radiates through to the back usually beneath the right scapula and sometimes to the right shoulder The duration of the attack is variable rarely more than several hours often less Vomiting is usual and in many instances brings some degree of relief In some cases the attacks recur very frequently in others after an intermission of months or even years Fever and leukocytosis may or may not occur depending upon the presence and degree of infection in the gallbladder if there is a stone in the cystic duct or in the bile ducts if the stone is in the common duct Slight or moderate icterus may be noted The urine often contains bilirubin within a few hours after the attack This is a regular occurrence with common duct calculus and is the basis for the important history of temporarily dark urine The stools are often light in color for from one to several days

Complications —Internal biliary fistulae may open into the colon duodenum or rarely the pylorus also into the peritoneal or pleural cavities and the skin Cholecystoduodenal fistulae permit passage of large stones into the small bowel where they may produce intestinal obstruction This is characterized by an irregular recurrence of vomiting and abdominal distention as the stone moves slowly along the small bowel stopping at intervals until propelled further by increased peristalsis

There are other complications in which both gallstones and associated infection play a common role *i e* pancreatitis both acute and chronic peritonitis due to perforation of the gallbladder cholangitis and liver abscesses pylephlebitis rarely thrombosis of the hepatic vein or endocarditis

Diagnosis —The dyspeptic symptoms due to stones in the gallbladder must be distinguished from those of *peptic ulcer* Relief from food milk or soda is rarely noted to any distinct degree in cases of gallstones but is fairly characteristic of ulcer The distress of ulcer is usually located in midepigastrium while that due to gallstones is as a rule in the right upper quadrant of the abdomen Dull pain caused by an irritable *spastic colon* may be noted at times in the area of the gallbladder this is usually distinguished on the basis of the history of marked constipation or diarrhea relief of distress following bowel movement and the occurrence of pain at other times in the region of the cecum splenic flexure or sigmoid colon Spastic colon and gallstones may be present in the same individual and

necessarily infective carriers) In the mixed stones, the proportion of the different chemical components is quite variable in different cases cholesterol nearly always predominating to a marked degree Calcium may be deposited as a shell about a stone composed of cholesterol and calcium bilirubinate This is especially true in cases of cystic duct obstruction due to another stone Such stones are distinctly radiopaque Stones containing calcium bilirubinate are more difficult to visualize by x ray, while pure cholesterol is not distinguished except under optimal conditions by contrast with the dye used in cholecystography

Symptoms and Signs—The symptoms of gallstones are dependent in considerable measure upon their location Stones in the gallbladder probably produce symptoms by virtue of pressure or irritation of the wall of the viscus Colicky pain such as characterizes stones in the ducts is not produced Vague sensations of fulness dull distress in the epigastrium or right upper quadrant, especially after eating, also pyrosis sour eructations and flatulence are very suggestive of gallbladder stones Distress is often more noticeable after certain foods are eaten notably pork cabbage, or fried foods Other individuals however with proved gallstones, may not observe any qualitative food distress The amount of food may or may not be of significance, in various instances although it is commonly noted that attacks follow a heavy meal During pregnancy the symptoms are usually exaggerated presumably because of increased biliary stasis

The physical signs of gallbladder stones are few or none There may or may not be tenderness over the region of the gallbladder Rarely it is possible to palpate such stones especially if they compose a large mass adherent in the fundus of the thickened gallbladder

Stones occluding the cystic duct commonly produce biliary colic as described below The gallbladder is often distended at times enormously so with a thin watery mucus This distention is in contrast to the small or 'atrophied' gallbladders usually noted in patients having common duct stone (Courvoisier) Chronic cystic duct obstruction may result in "hydrops" of the gallbladder of such extent that even several liters of fluid are found in the viscus at operation or autopsy, and in these cases it may extend well down into the pelvis Of greater danger, however, is the accumulation of purulent exudate in the obstructed gallbladder This condition of empyema may result in gangrene and perforation with generalized peritonitis The gallbladder under these circumstances may dilate considerably even though the wall is markedly thickened This is simply because of the considerable increase in intraluminal pressure plus inflammatory softening of the gallbladder wall A further discussion of this condition is found below under the heading of acute cholecystitis

Stone in the Common Duct—More often than not common duct calculi are multiple Pain is produced when the stone or stones first enter the duct, following which there is stretching and smooth muscle spasm in an attempt to expel the stone As the duct dilates colic may disappear until such time as a stone enters the ampulla of Vater when smooth muscle contraction again produces pain which is often intermittent as the stone moves up and down in the lower end of the duct A ball valve action of this type usually results in jaundice of fluctuating intensity and is often productive of suppurative cholangitis with chills and fever The latter has been spoken of as 'hepatic intermittent fever (Charcot Osler) The fever abates when bile drainage is reestablished and recurs as the stone reenters the ampulla Disappearance of fever and jaundice is usually not due to expulsion of the stone through the ampulla More often this is simply due to a shift in position of the stone within the duct Expulsion occurs at times however and in these cases the stone may be recovered from the stools Except where the diagnosis of cholelithiasis is in doubt examination of the stools for gallstones has relatively little value since the finding of a stone gives no clue as to how many remain in the common duct or gallbladder In doubtful cases the stools should be strained for stones after repeated duodenal instillation of magnesium sulfate (See later)

Stones Impacted in the Ampulla of Vater—This condition is characterized by chronic jaundice and as a rule marked pruritus Pain is often absent but there is usually a history of colicky pain prior to the appear

and Cole) If given in the evening x ray the following morning will reveal the shadow due to concentrated dye within the gallbladder A fatty meal or an egg yolk meal (Boyden) results in prompt contraction of the size of this shadow if the gallbladder function is normal If the cystic duct is occluded or if the gallbladder has entirely lost its concentrating function there may not be a sufficient concentration of dye to permit of contrast with cholesterol stones in this event the condition can be classified only as a non functioning gallbladder in which stones may or may not be present An upright film is occasionally of value in demonstrating cholesterol stones not otherwise evident In the upright position the stones may be concentrated in a layer near the fundus of the gallbladder Cholecystography is probably about 90 per cent efficient in the demonstration of gallstones Duodenal drainage (Lyon) is often confirmatory in doubtful cases it rarely yields positive information where x rays are negative although the converse is often noted (Doran)

Biliary colic is usually recognized without difficulty *Renal* and *intestinal colic* rarely cause confusion The pain of renal colic commences in the loin or flank and radiates downward especially to the inner surface of the thigh or to the genitalia dysuria and hematuria are often present The pain of intestinal colic (including lead colic and acute porphyria) is usually a more generalized crampy pain often somewhat more marked below the level of the umbilicus If due to intestinal obstruction there is increasing emesis distention of the abdomen and the auscultatory finding of high pitched or musical borborygmi in association with the colicky pain If due to *lead colic* the occupational history the presence of a lead line on the gums and the finding of basophilic stippling in the red blood cells are all of aid in diagnosis The colic of *acute porphyria* may closely simulate gallstone colic the presence of red urine due to porphyrin (or of urine that becomes red on exposure to light) is of decisive importance

The pain of acute *coronary thrombosis* may be confused with that due to gallstones In some cases coronary thrombosis is productive of abdominal distress only and this may be limited to the right upper quadrant or epigastrium The electrocardiogram is of much aid in such instances The presence of a pericardial friction rub is distinctive. Slight jaundice may follow an attack of coronary thrombosis but is less common than with biliary calculus and does not appear as a rule until several days after the attack when it is often but not always associated with pulmonary infarct Jaundice and dark urine (bilirubinuria) usually appear within twenty four hours after a gall stone colic if at all Urobilinogenuria is usually noted shortly after a gallstone attack but is delayed for from forty eight to seventy two hours following a coronary thrombosis *Biliary dyskinesia* (or dyssynergia) without gallstones is undoubtedly productive of biliary colic in rare instances This term indicates a simultaneous spastic contraction of the gallbladder and sphincter choledochus with resultant colicky pain The cause of the condition is not clear There can be little doubt that persistent distress after cholecystectomy especially where stones were not found is at times due to recurrent spasm of the sphincter of Oddi Biliary dyskinesia is recognized by the fact that cholecystokinin or substances such as egg yolk which stimulate its production cause spasm of the sphincter of Oddi With the duodenal tube in position no bile can be obtained but after instillation of magnesium sulfate dark bile appears and the pain promptly abates (Ivy) Dyskinesia is not to be considered unless gallstones have been excluded by all possible means

Marked jaundice due to *impacted stone* is at times confused with jaundice due to cancer of the biliary tract including carcinoma of the head of the pancreas A previous history of gallstone colic and jaundice is suggestive of calculous jaundice but it must be borne in mind that cancer of the bile ducts is relatively common in individuals with gallstones Loss of weight is usually more profound in the presence of cancer of the biliary tract than in jaundice due to stone The following features are of particular aid in distinguishing these conditions (1) The presence of complete biliary obstruction as denoted by the finding of less than 5 mg of fecal urobilinogen per day with less than 0 3 mg of urobilinogen in the twenty four hour urine This finding is

there is little doubt that gallstones aggravate irritability of the colon

Gallbladder stones are but rarely palpable and even in such instances, diagnosis must be confirmed by x ray Palpable stones usually contain enough calcium to permit visualization by means of a simple flat plate of the gallbladder region Cholecystography is often necessary for the diagnosis of gall stones particularly those composed chiefly of cholesterol with little or no calcium This method depends simply upon excretion of tetraiodophenolphthalein by the liver into the bile with subsequent concentration in the gallbladder The dye may be given by mouth quite satisfactorily It is absorbed into the portal circulation and about 96 per cent of it is excreted in the bile (Graham

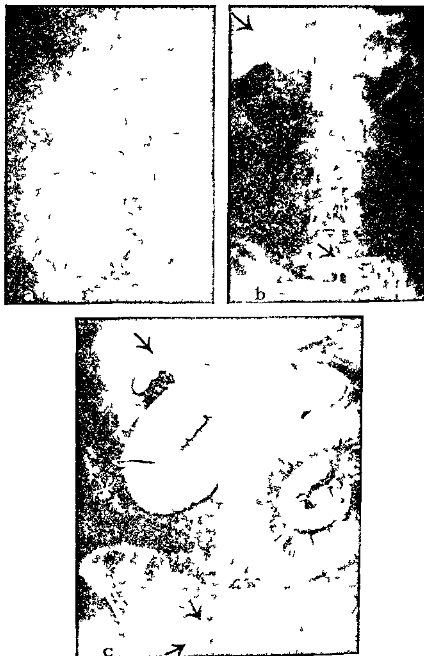


Fig 81 —*a* Mass of calcified gallstones in the gallbladder as noted on 7/22/31 *b* 8/18/32 Patient now has symptoms of bowel obstruction Upper arrow indicates gas in the biliary ducts (due to cholecystoduodenal fistula) Lower arrow indicates the mass of calcified gallstones now in the small bowel *c* After barium meal upper arrow indicates cholecystoduodenal fistula Lower arrows indicate gallstones in the small bowel. Note distended loops above (Borman and Rigler Surg 51 1937)

tapioca later vegetables Baked or mashed potato spinach carrots, string beans asparagus lettuce celery squash are tolerated best Onions sauerkraut cabbage turnips radishes or cucumbers may cause recurrence of distress Lean meat including roast or boiled chicken beef or lamb may be eaten in moderation Baked or boiled fish is usually tolerated Butter and cream should be taken but sparingly, vegetable fat particularly olive oil probably has a beneficial effect in stimulating bile flow without being productive of distress

Bile salts are distinctly beneficial They should be used in fairly pure form not simply as dehydrated bile which may induce nausea and distress Given in an amount of 3 to 6 grains (0 2–0 4 Gm) three times daily bile salts often appear to prevent recurrences of symptoms for long periods of time Occasional cases have been observed in which multiple gallbladder stones disappeared after a long course of bile salt therapy

For relief of biliary colic nitroglycerin or amyl nitrite inhalations should first receive trial If nitroglycerin is used a tablet of hypodermic type $1/100$ grain (0 00065 Gm) is placed beneath the tongue and allowed to dissolve At the same time sodium phenobarbital 2 grains (0 13 Gm) may be given subcutaneously Prompt relief is often afforded by these measures In some cases it will be necessary to use morphine sulfate $1/6$ to $1/4$ grain (0 01–0 016 Gm) by hypodermic although there is little doubt that morphine increases spasm of the sphincter choledochus thus increasing intrabiliary pressure (Walters Bergh and Layne) While morphine has been employed for many years in the treatment of biliary colic and is still necessary in many instances its analgesic effect in these cases is central and not local and it is not improbable that the resulting increase in intrabiliary pressure is undesirable

Milder attacks of colic are at times allayed simply by rest the application of hot compresses to the abdomen and the evacuation of gas by means of a tap water enema

In cases of calculous jaundice repeated duodenal instillation of magnesium sulfate on three or four successive days is advisable The icterus may abate rapidly with the result that the patient is in better condition for operation

The treatment of pruritus associated with jaundice is not particularly gratifying Calamine lotion or carbolic lotion 1 60 are of aid in some cases If it is known that the patient is not sensitive to novocain very gratifying results are at times noted following intravenous administration of $1/6$ grain (0 010 Gm) or 10 cc of a 0 1 per cent solution At times this may be the only means of permitting the patient to sleep through the night

Surgical—Adequate preoperative preparation is of utmost importance This is particularly true in jaundiced patients The prothrombin time (Quick) should be determined and if significantly prolonged *vitamin K* together with bile salts are given If the prothrombin time is prolonged synthetic 2 methyl 1 4 naphthoquinone may be given either by mouth or intravenously This substance is even more effective than natural vitamin K which has the disadvantage of being insoluble in water There are several water soluble preparations of the synthetic naphthoquinone on the market which are entirely satisfactory It is unnecessary to use bile salts with these whereas this is essential with the natural fat soluble vitamin K Given by mouth an amount of 5 mg daily is adequate If given intravenously 1 mg of the active material per day suffices The response of the prothrombin time to intravenous injection is of considerable diagnostic and prognostic value In general it may be said that with relatively good liver function the prothrombin time will return to the control level within six hours after intravenous administration of 1 mg with poor liver function especially with primary diffuse liver damage the prothrombin time is unlikely to return to the normal range

Operations on the biliary tract should be preceded by a diet plentiful in protein and carbohydrate and low in fat In general this diet should consist of approximately 300 Gm of carbohydrate 100–150 Gm of protein and a minimal amount of fat (30–40 Gm) If the patient is unable to eat a regular diet it may nevertheless be possible to give frequent liquid feedings consisting of skim milk fortified with a powdered food of

noted in over 90 per cent of cases of cancer of the biliary tract and in less than 10 per cent of the cases of calculous jaundice (Watson) (2) The palpation of a smooth nontender distended gallbladder This is frequently possible in cases of cancer of the biliary tract, but rare in jaundice due to stone in the common duct Courvoisier found that the gallbladder was atrophied in 70 of 87 cases of calculous jaundice, as contrasted with 17 in which it was dilated This dilatation was marked in but 2 cases These figures related to observations at operation or autopsy The clinical value of palpating a distended gallbladder is probably even greater than Courvoisier's figures indicate In the writer's experience, a distended gall bladder of the type mentioned above has not been palpated in cases of jaundice due to calculus in the common duct When found in association with complete biliary obstruction the diagnosis of cancer of the biliary tract is relatively certain

Parenchymal jaundice may be confused with calculous jaundice The term parenchymal applies to diffuse cellular liver damage such as occurs with cirrhosis acute or subacute atrophy and in many cases of so called 'catarrhal jaundice In distinguishing jaundice due to *cirrhosis* the following features are of importance the history of chronic alcoholism of ingestion of drugs such as cinchophen or arsenic of arsenical therapy for syphilis or of a previous attack of painless jaundice the presence of a small liver with or without ascites the development of collateral circulation over the abdomen enlargement of the spleen hematemesis and demonstration of esophageal varices by x ray, the presence of *spider nevi* in the areas of the body drained by the superior vena cava In *acute atrophy* the outstanding differential features are progressive increase of painless jaundice, demonstrable decrease in the size of the liver early appearance of somnolence and coma the 'fetor hepaticus or amine odor a peculiar musty sweetish and very pervading aromatic odor quite characteristic of diffuse necrosis of the liver (Eppinger) This odor is noted at times in cases of advanced cirrhosis of the liver, and has also been observed in lesser degree in occasional cases of protracted severe catarrhal jaundice The latter condition is distinguished from calculous jaundice by virtue of the absence of colic the characteristic urobilinogenuria which often disappears briefly at the height of the icterus, then reappears rapidly and in marked degree as convalescence begins the positive galactose tolerance test A negative result of the galactose test is without significance however, especially after the jaundice has been present for more than a few days

Prognosis —Cholelithiasis of itself is rarely fatal but death may be caused by complications such as perforation of the gallbladder cholangitis liver abscesses or acute pancreatitis

Treatment —The choice of medical or surgical treatment of gallstones depends chiefly on the patient's general condition as well as on his or her wishes in the matter Cholecystectomy is the procedure of choice in cases where the presence of gallstones is proved Operation should not be undertaken simply because of pain presumed to be due to gallstones or gallbladder disease Operation may be deemed inadvisable in proved cases because of advanced age cardiac failure renal insufficiency or other serious disease In the usual case however cholecystectomy is indicated because of the many serious complications which gallstones may produce Cases of cholelithiasis when not treated surgically are apt to have recurrent attacks in spite of medical management operation has often been postponed until some dangerous complication has appeared and the patient may now have reached an age which in itself materially increases the risk Furthermore the important relation of cholelithiasis to the occurrence of primary cancer of the biliary tract must be taken into account

Medical —Control of the diet is of prime importance Foods high in cholesterol such as fat and eggs should be eliminated or greatly reduced Greasy or fried foods pork products rich dressings and cheese spicy foods, and alcoholic beverages are most likely to cause exacerbation of symptoms Immediately after an acute attack it is desirable that the diet be limited to liquids such as skim milk milk soups and strained orange juice in small amounts After a short time cereals may be added then rice and

CHOLECYSTITIS

Etiology —The age and sex incidence parallels that of cholelithiasis except in typhoid epidemics in which acute cholecystitis may occur in children of both sexes It is probable that acute cholecystitis is usually infectious in origin less often chemical This is still a matter of dispute The acutely inflamed gallbladder however does not always contain demonstrable bacteria (Andrews) Regurgitation of pancreatic juice into the biliary tract may at times play a role The large majority of cases of acute cholecystitis are associated with cholelithiasis and it is probable that gallstones are of much importance both from the standpoint of obstruction and stasis as is trauma to the mucosa

Acute cholecystitis may occur without gallstones This is noted particularly as a complication of about 1 per cent of cases of typhoid fever but may also be encountered in the wake of other acute infections

Members of the colon typhoid group are found most commonly when the contents of the acutely inflamed gallbladder are cultured The staphylococcus pneumococcus or streptococcus are present much le s frequently It is probable that these organisms gain access to the gallbladder either by way of the blood stream or by ascent from the duodenum Statistics as to which is the most frequent route are not available

Chronic cholecystitis is to be regarded as the quiescent stage of the disease after subsidence of acute manifestations Subsequent acute attacks are apt to occur There is usually but not always an associated cholelithiasis

Morbid Anatomy —Acute cholecystitis varies in degree from a mild catarrhal type to an extremely dangerous phlegmonous or gangrenous form In the mild catarrhal form the gallbladder is often moderately distended the serosa exhibits injection of the blood vessels the wall is somewhat tense and swollen and the mucosa is congested at times revealing small amounts of fibrinopurulent exudate on its surface Microscopically congestion and a moderate exudation of polymorphonuclear leukocytes in the submucosa and outer coats are observed



Fig 82 —*a* Cholangiogram taken with T tube in common bile duct Arrow indicates residual stone in lower end of duct *b* After removal of stone at a secondary operation (Courtesy of Dr Leo G Rigler)

The *phlegmonous* type is characterized by marked thickening of the gallbladder wall at times attaining more than 1 cm As a rule the cystic duct is obstructed by stone and the resulting pressure within the gallbladder is sufficient to cau e distention which may be considerable in some cases The increase in pressure plus softening of the wall or outspoken gangrene constitute the chief dan

high protein and carbohydrate content Foods of this type are available which contain 35–40 per cent protein and 60–65 per cent carbohydrate and which are at the same time rich in minerals and added vitamins When mixed with skim milk a food value of 1000 calories per liter or more can be attained The studies of Ravdin and of Whipple and his associates reveal clearly that an adequate intake of protein is essential to the protection of the liver While there is no doubt that glucose is of value, it is quite insufficient in many instances to prepare patients for operation simply by giving them intravenous glucose as is often customary This is especially true if the patient is malnourished febrile toxic or markedly obese Such individuals are apt to have fatty livers a factor of great importance in operative mortality The amount of glucose that is given intravenously is often not enough to supply the patient s caloric needs much less to convert the fatty liver into one filled with glycogen Further than this the preoperative preparation should include if at all possible a plentiful supply of vitamins especially B complex Choline and riboflavin deficiency in particular have been implicated with respect to fatty infiltration of the liver It is probably best to give these patients crude sources of B complex either brewer s yeast in amounts of 30–40 Gm daily or relatively crude liver extract fortified with the known components such as thiamin niacin and riboflavin The dosage of such preparations is empirical but it should probably not be less than 8 or 10 capsules daily

Cholecystectomy in cases of proved gall stones effects a cure in most instances The operative mortality rate is very low in the hands of experienced surgeons usually not exceeding 1 5 per cent The fatality figure is higher for operations on the common duct

Secondary operations are necessary at times because of postoperative stricture unrecognized common duct stone reforming of stones in the hepatic or common bile ducts adhesions or hernia Common duct calculi are apt to be overlooked unless the common duct is opened and explored This should be done if the patient is or has been jaundiced assuming that operation has been decided upon If possible it is wise to have a cholangiogram made at the time of operation, before the abdomen is closed After stones have been removed from the duct, T-tube drainage should be carried out for a period of months Before the T tube is removed from the duct a *cholangiogram* should again be made This consists of injecting a radiopaque material usually 50 per cent diadrast, into the T tube then taking an x ray film of the area of the common duct and ampulla Cholangiograms at times reveal unsuspected stones which were overlooked at operation in spite of opening the common duct Best has described procedures intended to expel these stones into the duodenum These include the injection of magnesium sulfate solution and of olive oil into the T tube also the use of nitroglycerin

Failure of cholecystectomy to relieve symptoms is much more common in cases where gallstones were not demonstrated either before or during operation Some of these cases at least belong in the *biliary dyskinesia* group

C J Watson

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in the right lower quadrant rarely higher usually serves to distinguish appendicitis Right *pyelonephritis* at times simulates cholecystitis with respect to pain The maximal tenderness however is usually in the loin and this fact plus the urinary symptoms and findings make differentiation possible

Prognosis—Except for complications such as perforation and peritonitis pancreatitis or liver abscess the chances for immediate recovery are excellent Subsequent attacks however are likely to occur

Treatment—In the milder forms rest in bed liquid diet heat to the abdomen, and sedatives usually result in rapid disappearance of symptoms In the more severe forms the question of surgical intervention is often a difficult one Some believe that cholecystectomy should be performed in the early stage of every case of acute cholecystitis In general however it is probably wiser to adopt conservative measures at the outset since the large majority of cases respond well and operation may then be carried out with relative safety during a quiescent stage After the acute symptoms have subsided it is desirable to wait several weeks before surgery is undertaken If conservative measures fail to bring some degree of improvement within two to three days and the severity appears to be such that perforation is feared the procedure of choice is cholecystostomy Extirpation of distended empyematous gallbladders is not advisable In older individuals where circulatory complications are often present it may be possible simply to drain the gallbladder under local anesthesia Later depending upon the patient s general condition cholecystectomy may be indicated

Conservative measures during the acute stage include hot moist compresses to the abdomen sedation by means of sodium phenobarbital subcutaneously (2 grains [0 13 Gm] at intervals of four to six hours) and morphine 1/6 to 1/4 grain (0 01–0 016 Gm) if necessary to relieve severe distress Nasal suction siphonage may be necessary for abdominal distention and vomiting In the severer cases nothing other than ice chips should be given by mouth Infusions of 5 per cent glucose in saline may be administered subcutaneously and intravenously As the attack subsides liquids by mouth may be started and the diet as already described under the treatment of gallstone colic may be instituted

The treatment of chronic cholecystitis depends on several factors the most important of which is the presence of gallstones If these are demonstrated cholecystectomy is usually the procedure of choice This will depend again upon the patient s age and general condition the operation should not be carried out in the presence of any serious constitutional disease such as myocardial or renal insufficiency If there have been repeated distinct attacks of acute cholecystitis even though stones cannot be demonstrated cholecystectomy is usually indicated during a quiescent period Conservative treatment is to be preferred however in patients who complain only of dyspeptic symptoms and in whom the cholecystogram has revealed nothing more than a reduced gallbladder function There can be no doubt of the rare occurrence of mild chronic cholecystitis with apparently normal gallbladder function as determined by cholecystography The symptoms in these cases are probably often on the dyskinetic basis although there is good evidence that biliary dyskinesia also exists without any demonstrable pathologic change in the gallbladder or ducts The results of operation in this group of cases are usually disappointing Distress frequently recurs Conservative treatment consisting of the diet already suggested for the management of cholelithiasis together with bile salts often enables the patient to avoid distress The use of magnesium sulfate is at times beneficial probably because of its relaxing effect on the sphincter of Oddi

C J WATSON

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gers of this disease, i e perforation and peritonitis This occurs with relatively greater frequency in patients more than sixty years of age The inflammation in most cases subsides without perforation If the cystic duct remains closed the distention of the gall bladder may persist either as a low grade or subsiding empyema, or a hydrops

In phlegmonous or acute suppurative cholecystitis, microscopic examination shows a very diffuse exudate throughout the entire wall composed of polymorphonuclear leukocytes and fibrin Necrosis may be noted and is prominent in the gangrenous type In chronic cholecystitis perivascular foci of lymphocytes are seen in the serosa there is often moderate thickening of the gall bladder wall with some increase of connective tissue and extensive adhesions to adjacent organs *Cholesterosis* or straw berry' gallbladder may be secondary to low grade subacute or chronic inflammation In this condition, cholesterol esters are deposited just beneath the mucosa and are seen grossly as numerous yellowish granules or streaks The exact nature of cholesterosis is as yet unknown

Symptoms and Signs—The symptoms of chronic cholecystitis cannot be distinguished from those of stones in the gallbladder The manifestations of acute cholecystitis are in proportion to its severity In the mild catarrhal form there may be nothing more than indigestion moderate pain and tenderness in the right upper quadrant of the abdomen slight fever and malaise With more severe degrees of infection there is more marked pain and tenderness and muscle spasm is elicited Rebound tenderness in the right upper abdomen is noted in the more severe cases of suppurative cholecystitis The spread of pain tenderness and rebound tenderness over the abdomen generally indicates either that perforation has occurred or that there is an associated pancreatitis with areas of fat necrosis in the omentum and mesentery The gallbladder is at times palpable in acute cholecystitis As a rule it is rather vague and difficult to outline principally because of tenderness and muscle spasm At times however the gallbladder is felt more distinctly as a very tender sausage like mass extending down below the right rib margin slightly lateral to the midclavicular line This type is more often palpated in patients suffering their first attack of cholecystitis where there has not been previous thickening of the gall bladder wall for example with typhoid fever

Marked prostration often results from acute suppurative cholecystitis The mouth temperature is commonly elevated to from 102° to 104° F Nausea and vomiting are frequently observed Abdominal distention (ileus) is not uncommon Jaundice may be present and if at all prominent indicates calculous obstruction of the common duct or the hepatic ducts Slight jaundice is due in some cases to associated liver damage which results from the infection spreading via the lymphatics into the liver The urine commonly contains increased amounts of urobilinogen which usually disappear within twenty four to forty eight hours after the infection subsides As a rule the attack of cholecystitis is of relatively short duration from a few hours to a few days In some instances however, empyema of the gall bladder may produce persistent pain and tenderness for weeks A somewhat vague tender mass representing the subacutely inflamed gallbladder may be felt for an equal period of time eventually becoming smaller and less tender, until finally it is no longer palpable During the stage of acute inflammation, the leukocyte count is elevated to from 12 000 to 40 000 usually about 15 000 This is a neutrophilic leukocytosis It is often of value in determining the severity of the infection particularly with reference to the question of operation, to follow the percentage of band forms or the filament nonfilament ratio

Diagnosis—The location and character of the pain and the history of previous attacks of gallstone colic or jaundice are helpful in distinguishing cholecystitis from *ulcer* After perforation has occurred the symptoms and findings may be identical The presence however of free gas in the peritoneal cavity, as determined by x ray is more likely to indicate perforation of the gastro intestinal tract rather than of the gallbladder *Acute appendicitis* particularly in individuals with a high lying cecum may offer difficulty The history of onset of diffuse abdominal pain with subsequent localization

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CARCINOMA OF THE GALLBLADDER AND BILE DUCTS

Etiology and Occurrence—Carcinoma of the gallbladder is usually associated with gallstones and is consequently observed more frequently in females Carcinoma of the bile ducts is slightly more common in males nevertheless gallstones are not infrequently associated with this condition In general there can be little doubt that chronic irritation due to gallstones and associated infection is an important factor in the initiation of cancer of the gallbladder and to a lesser degree of the bile ducts

Morbid Anatomy—Carcinoma of the gallbladder may originate in any part of the viscus If primary in the fundus direct extension into the liver is common tumors primary in the corpus or collum often invade the bile ducts These differences in origin are of importance with respect to the presence or absence of icterus also to the type of mass palpable in the gallbladder area during life Tumors primary in the collum may cause simple distention of the gallbladder while tumors of the fundus are often responsible for a hard nodular mass Of interest is the fact that the gallbladder may be found to be markedly distended if the cystic duct is obstructed by a tumor This is quite comparable to what has already been discussed in connection with calculous obstruction of the cystic duct although the inflammatory changes with cancer are usually much milder in these cases the lumen of the gallbladder is filled with thin white mucus In some instances carcinoma obstructing the cystic duct may bleed into the lumen of the gallbladder thus causing marked distention Microscopically the tumor may be either carcinoma simplex adenocarcinoma or squamous cell carcinoma (metaplasia)

Carcinoma of the bile ducts is often of the scirrhous type and may be so small as to be confused with a benign fibrous stricture Microscopic examination in such instances reveals nests of cancer cells interspersed with fibrous tissue Suppurative cholangitis is seen at times above a primary carcinoma of the common duct or of the cystic duct at its junction with the common hepatic duct Primary carcinomata are relatively frequent at this point They may also occur in the lower end of the common duct In rare instances soft polypoid carcinomata occur within the common duct and may exhibit ball valve activity much like a stone in the common duct

Symptoms and Signs—Most of the cases have had previous symptoms of gallstones or cholecystitis Carcinoma of the fundus of the gallbladder produces dull constant pain and often tenderness weakness and loss of weight and a hard nodular mass in the region of the gallbladder Jaundice is usually present but may appear relatively late Once established it deepens progressively and complete biliary obstruction (less than 5 mg of fecal urobilinogen per day) usually occurs Jaundice appears relatively early with carcinoma of the corpus or collum of the gallbladder and it is usually the first symptom of primary carcinoma of the ducts In some instances the latter may be masked by the presence of colic chills and fever due to obstruction and cholangitis The jaundice occasionally disappears due to establishment of an internal biliary fistula

The liver may be enlarged and nodular with any of these primary carcinomata Enlargement due to metastases is somewhat more commonly encountered in cases of cancer of the gallbladder Ascites is noted at times due to peritoneal involvement As these conditions progress there is deepening jaundice cachexia and often a hemorrhagic tendency Somnolence and coma the cholemic state usually precedes death The hemorrhagic tendency is due at least in part to prothrombin deficit (prothrombin time often two to three times that of the normal control) The jaundice may be of a deep olive type this is said to be due to formation of biliverdin within the bile ducts for which oxidative ferments liberated from the tumor cells are held to be responsible Biliverdin icterus is strongly suggestive of carcinomatous biliary obstruction although at times it is seen in cases of jaundice not due to cancer

Diagnosis—The presence of *complete*

SUPPURATIVE CHOLANGITIS

Etiology and Occurrence —Suppurative *cholangitis usually results from biliary stasis* due to stone or neoplasm, in individuals who have had previous infection of the biliary tract The condition is observed most often with common duct calculus but is also seen at times with carcinoma of the gallbladder or bile ducts In the latter cases of cholangitis there is nearly always an associated cholelithiasis In contrast with these are the cases of carcinoma of the pancreas with biliary obstruction, in which cholangitis is relatively rare and in which there is usually not an associated cholelithiasis or previous biliary tract infection Various pyogenic organisms are responsible for suppurative cholangitis The colon bacillus and streptococcus are most common Very often these are present in the biliary tract prior to the onset of biliary stasis In other cases the infection of the obstructed bile ducts is probably hematogenous, although this is a matter of some doubt The occurrence of suppurative cholangitis in the absence of biliary obstruction is extremely rare

Morbid Anatomy —The bile ducts both intrahepatic and extrahepatic are dilated above the area of obstruction, which is usually in the common bile duct The ducts are also thickened because of inflammatory changes In the liver there is periportal inflammation often actually small abscesses *The periportal involvement is frequently of* chronic suppurative type in cases of cholangitis due to calculous obstruction Microscopically the small bile ducts are seen to contain polymorphonuclear leukocytes, and these are also found in variable number together with plasma cells and lymphocytes *in the adjacent portal areas*

The term 'cholangitis lenta' signifies a hematogenous form of suppurative cholangitis of grave prognosis due to a streptococcus Secondary endocarditis may occur (Pepper)

Symptoms and Signs —Jaundice with or without colicky pain chills and irregular but marked fever usually of spiking type are the outstanding features of suppurative cholangitis The liver is usually enlarged and moderately tender The spleen is occasionally palpable There is marked neutrophilic leukocytosis The urine contains bilirubin and as a rule much urobilinogen The blood culture may be positive

Complications —Metastatic abscesses may occur Hemorrhage from the mucous membranes is likely to result from prothrombin deficit, if this is not corrected by administration of vitamin K Hepatic coma is apt to precede death which is due to severe liver damage and insufficiency, together with generalized toxemia

Diagnosis —Suppurative cholangitis is likely to be present in any patient having jaundice chills fever sweating an enlarged tender liver, and leukocytosis especially if that patient has had previous jaundice or gallstone colics Liver abscesses due to other causes, and suppurative pylephlebitis may give rise to confusion The latter is suggested if there is free fluid in the abdomen The stools should be examined carefully for amebae in order to exclude amebic abscess *of the liver Duodenal drainage may establish* the presence of suppuration in the bile ducts

Prognosis —The prognosis is grave but not necessarily fatal If it is possible to establish adequate drainage recovery may occur

Treatment —Temporary spontaneous improvement not infrequently occurs particularly in the calculous cases in which obstruction is often partially relieved by the shifting position of a common duct stone It is *therefore best to support* the patient for several days with fluids and glucose parenterally The general condition may be improved by giving vitamins especially B complex and K (2 methyl 1 4 naphthoquinone) parenterally together with protein either in liquid form by mouth or as *plasma transfusions* Transfusion of blood is desirable if there is anemia or profound toxemia Operation should probably not be delayed for more than one week unless the infection is definitely subsiding At the end of this time T tube drainage of the common dust is usually advisable In some cases the surgeon may deem it sufficient to drain the gallbladder only if it can be established that the cystic duct is not obstructed

This subject is discussed in the section on Diseases of the Liver (p 751)

C J WATSON

are recurrent attacks of jaundice and often of paroxysmal pain associated with a palpable cystic tumor and appearing in childhood (McWhorter) The treatment is surgical

C J WATSON

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DISEASES OF THE PANCREAS

BECAUSE of the many important functions of the pancreas some of which are associated with those of other parts of the alimentary tract diseases of the pancreas were for many years confused with those of the stomach liver and intestinal tract The modern history of the study of the diseases of the pancreas begins with the contribution of Friedreich published in 1857 The knowledge of such phases of the pathology of the pancreas as gangrene fat necrosis hemorrhage acute and chronic inflammation and the relation of the pancreas to diabetes gradually increased during the following three decades Chiari in 1876 described a case of sequestration of a gangrenous pancreas Balser in 1882 was the first to describe accurately fat necrosis as seen in the pancreas and adjacent fatty tissue American pathologists added to the subject when in 1886 Draper described pancreatic hemorrhage as the cause of sudden death and Reginald Fitz in 1889 clearly established the clinical entity of acute pancreatitis In the same year von Mehring and Minkowski published their classic paper on the relationship of diabetes mellitus to the internal secretion of the pancreas

Since that time the elaborate monographs of Oser Opie and Mayo Robson the work of Sweet and the epoch making contribution of Banting in perfecting insulin in the treatment of diabetes have brought the subject to its present position of importance in both medicine and surgery

Pathogenesis —Before classifying the diseases of the pancreas it is essential to point out certain facts in the physiology and pathology of the pancreas The pancreas has both an internal and an external secretion The former has to do with the metabolism of carbohydrates which is apparently the one vital function of the pancreas The external secretion collected by a duct system and emptied as pancreatic juice into the duodenum contains the proferments or zymogens which when activated have to do with the digestion of proteins, fats and carbohydrates The most potent stimulant of the production of pancreatic juice is secretin which is absorbed from the duodenum and carried by the blood to the pancreas The two constituents of the pancreatic juice most important in the study of pancreatic disease are the trypsinogen and steapsinogen These are inactive in the ducts and parenchyma of the organ but when activated are powerful ferments The normal activating agent for trypsinogen which transforms it at body temperature immediately into trypsin is the enterokinase produced by the cells of the mucosa of the small intestine Steapsinogen on reaching the duodenum is normally transformed by some constituent of the bile into the fat splitting ferment steapsin

Infection or trauma may cause activation of the zymogens of the pancreatic juice in the gland itself or in the adjacent tissues and thus gives rise to the characteristic and pathognomonic lesions of protein and fat autodigestion which are seen at operation or autopsy and to the various grades of inflammation described as acute pancreatitis Acute lesions are the result of the action of both these ferments but the distressing and often fatal disturbances which accompany such changes are due to the proteolytic digestion of the blood vessels and living protein of the pancreas and adjacent tissues Thus the action of trypsin is all important in the etiology of these acute lesions From the experimental work of Sweet and others it would seem that, in the acute lesions trypsinogen is transformed into trypsin by an activating substance produced by autolysis of the pancreatic tissue An injury sufficient to produce local necrosis and subsequent autolysis of pancreatic tissue with activation of trypsinogen may result from direct trauma hemorrhage (as in apoplexy of the pancreas) or acute bacterial infection Delezeune first demonstrated the

biliary obstruction as evidenced by less than 5 mg of fecal urobilinogen and 0 3 mg of urinary urobilinogen per day is usually indicative of cancer of the biliary tract This has been referred to in the discussion of calculous jaundice The icteric index is often over 100, while in calculous jaundice it is usually considerably under this level In the various forms of parenchymal jaundice the icteric index varies much more widely The importance of palpating a smooth non tender distended gallbladder may be noted again as favoring carcinomatous biliary obstruction This has also been referred to in the discussion of calculous jaundice

Postoperative *stricture of the common duct* must be distinguished from cancer of the ducts The history of onset of jaundice shortly after cholecystectomy usually serves to indicate the presence of the former condition In many cases the general condition remains relatively good in spite of long continued jaundice quite in contrast with the progressively downhill course of cancer of the bile ducts Traumatic stricture may or may not be associated with complete biliary obstruction, or with suppurative cholangitis Benign stricture of the common bile duct of nontraumatic origin is extremely rare (Walters)

Prognosis—Death usually occurs within a few months from the time of onset of symptoms

Treatment—If the disease is obviously not too far advanced, operation should be carried out In occasional cases it is possible to resect a small primary carcinoma of the common bile duct In one such instance observed by the writer the surgeon was able to remove all of the primary tumor so far as could be determined microscopically it was further possible to anastomose the remaining portions of the duct over a T tube This patient recovered from the operation and was relatively well for a period of eight months but subsequently died of metastases Such cases emphasize the need for early diagnosis and operation In patients where the tumor is inoperable anastomosis of the gallbladder to the stomach or small intestine may prolong life or at least bring relief from otherwise intractable pruritus

The preoperative preparation of these patients, especially the use of vitamin K is the same as already described for stone in the common duct except that duodenal drainage is not employed

C J WATSON

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CONGENITAL ABNORMALITIES OF THE BILE DUCTS

Congenital Obliteration—This condition is probably due to developmental aplasia The process is confined to the lower portion of the common bile duct in about 16 per cent of cases (Holmes), while in the remainder the ducts within the liver are also obliterated The disease is characterized by deep jaundice coming on shortly after birth and gradually increasing The stools are acholic, and contain not more than traces of urobilinogen The urine contains much bilirubin and no urobilinogen These features permit distinction from icterus neonatorum or erythroblastosis ('kernikterus') The liver is enlarged and usually exhibits obstructive or biliary cirrhosis The spleen may be palpable thus necessitating differentiation from congenital syphilis In addition to the positive Wassermann and other features of congenital syphilis the exclusion of bile from the intestinal tract is not as complete Surgical exploration should be carried out in the hope that the obliterative process is limited to the lower part of the common duct Even where operation has been successful however the result has been but temporary Infection of the biliary tract follows sooner or later upon anastomosis of the gallbladder to the stomach or small bowel

Congenital Cystic Dilatation of the Common Bile Duct—This is a rare condition which is probably related to localized obliteration or stricture of congenital origin In some cases no obstruction has been found The cystic dilatation usually involves the middle and upper parts of the duct The cyst at times attains the size of a full term fetus Clinical features suggesting this condition

Presbyterian Hospital New York City the fulminating hemorrhagic form the suppurative type and abscess of the pancreas were associated with a cholangitis and chronic cholecystitis

Symptoms —In the hemorrhagic and diffuse suppurative types the onset which is sudden is characterized by agonizing and constant pain in the epigastrium or about the umbilicus with severe nausea and vomiting and symptoms of collapse A rapid pulse of low tension and an ashy cyanosis are not uncommon Extreme tenderness over the pancreas extending into the costovertebral angles when the retroperitoneal tissue is involved is characteristic The muscular rigidity is not as marked as in perforated ulcer of the stomach or duodenum In patients with the less fulminating lesions obstipation is common and the most frequent error in diagnosis is confusing it with acute intestinal obstruction

The constant agonizing pain the symptoms of collapse and the paralytic ileus have been explained as the result of stretching of the celiac plexus which is involved in the edematous peripancreatic tissue but the experiments of Sweet point to localized peritonitis and profound toxemia as the cause of the fulminating symptoms

The less severe forms of acute pancreatitis associated with edema of the pancreas and retroperitoneal tissue in the region of the pancreas frequently show symptoms of severe pain radiating to the back with tenderness across the pancreas but these forms as a rule do not produce the profound shock or the rapid pulse and cyanosis seen in some of the more severe forms

Diagnosis —Intestinal obstruction acute peritonitis due to the perforation of an ulcer or diseased appendix and acute cholecystitis are the conditions most frequently confused with acute pancreatitis In any obese individual giving a history of a heavy meal with alcoholic excess or of gallstone attacks or of the recurrent digestive disturbances of chronic cholecystitis acute pancreatitis should be suspected When such histories are given by patients who show extreme or even moderate tenderness over the pancreas there is sufficient evidence for diagnosis

Within the last few years attention has been called to the very important laboratory finding of an elevation of amylase in the patient s blood serum This is caused by a sudden blockage or compression of the duct of Wirsung or of the duct of Santorini as a result of edema or sudden blockage by calculus In some of the cases observed at the Presbyterian Hospital the serum amylase has been found to be as high as 130 units the normal being within the range of 15 to 30 units The finding of an elevated serum amylase in the presence of acute upper abdominal pain with tenderness across the upper abdomen points very emphatically to the diagnosis of acute pancreatitis

Treatment —De Takats has given a very excellent summary of the clinical picture of acute pancreatitis and has made a real contribution to the preoperative diagnosis and treatment He emphasizes the importance of preoperative management of the patient in shock as evidenced by low blood pressure and high red blood cell count with the administration of dextrose and insulin to combat the depletion of liver glycogen and the liver damage seen in these cases Dextrose should be given in a 10 per cent solution with Ringer s up to 100 Gm together with 20 to 30 units of insulin

The former emphasis by surgeons on the importance of immediate operation in all cases of acute pancreatitis is being modified at the present time in many clinics because it is now appreciated as a result of serum amylase studies and delayed operation that many patients recover without surgical therapy from mild attacks of acute pancreatitis particularly those associated with edema of the organ For this reason the author now feels that a more conservative attitude is justified in cases presenting a picture of pancreatitis If while under observation in a hospital the patient shows marked improvement after the above described therapy for shock and blood concentration it is justifiable to observe him for a few more hours noting the improvement in pulse color and signs of peritoneal irritation If later the patient shows a spread of peritonitis he is then in much better condition for operation and it can be done with far greater safety than it could with the patient in profound shock

At the time of operation the prime indication is for drainage of the infected fluid

presence in bacteria of an activating substance similar to enterokinase in its action on trypsinogen In recent years Dragstedt and his associates have produced convincing evidence that certain of the acute pancreatic lesions, commonly associated with bile invasion of the pancreatic ducts are the result of the destructive action of bile salts and that the bacteria in the ducts and pancreatic tissue especially the anaerobes growing in the damaged or necrotic tissue increase the damage and induce the toxic symptoms

Morbid Anatomy—It is evident that the degree of trypsin and steapsin digestion determines the pathologic findings at various stages of acute pancreatitis Lesions vary from an edema of the pancreas and retroperitoneal tissues and peritoneal exudate to extensive hemorrhage into the gland and peripancreatic tissue with necrosis of the gland and more or less fat necrosis in the pancreas and peritoneal fat according to the stage and severity of the disease In these lesions the activating agent of the steapsinogen is apparently independent of the activator in the bile It is the presence of typical areas of fat necrosis—round pearly white spots in the subserosa of the mesentery in the peritoneal fat and in the interlobular fat of the pancreas—that is always indicative of pancreatic disease The absence of such fat necrosis does not however rule out the possibility of acute pancreatitis Fat necrosis a dirty sanguineous exudate in the peritoneum, and edema induration, and enlargement of the pancreas are the most common abnormalities found at operation Usually all three and always at least two of these changes are seen during acute pancreatitis

If autolysis of the gland causes progressive hemorrhage necrosis and gangrene of more or less of the pancreas results Infection may be followed by varying degrees of edema and suppuration and by the formation of abscesses

Symptoms—In the severe types of pancreatic disease associated with necrosis and autolysis of the pancreas and hemorrhage into the gland there is an acute and fulminating toxemia often sufficiently severe to cause death within a few hours To Sweet belongs the credit of focusing the attention of the profession in this country on this dreadful intoxication—the *Pancreasvergiftung* of the Germans As a result of his experiments, corroborated by many investigators he has demonstrated that when the sterile excised pancreas of one animal is placed in the peritoneal cavity of another animal of the same or a different species the animal into which the pancreas is transplanted invariably dies with symptoms of profound toxemia Immediate autopsy reveals evidence of fat necrosis an irritative peritonitis most marked about the transplanted pancreas which is softened and disintegrating and a dirty peritoneal exudate The animal s own pancreas is not pathologically changed Sweet maintains and very logically that the pancreatic juice of the transplanted organ is the cause not only of autolysis of the host's tissue but also of the profound intoxication Whether this poison be elaborated by the destruction of the animal s own pancreas or within the transplanted pancreas the effects are the same

It is the quantity of this poison which determines the severity of the constitutional symptoms of acute pancreatitis and explains why in some cases the constitutional symptoms are so overwhelming when the anatomical changes are so slight

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ACUTE PANCREATITIS

Definition—*The term* 'acute pancreatitis" includes the hemorrhagic suppurative and gangrenous types

Occurrence—The disease appears to be most common in adult males who eat and drink heavily The fact that in many patients the onset occurs one or two hours after a heavy meal is explained by recalling that the pancreas is most active at that time and that any injury, such as a small hemorrhage or distention *of a duct* favors the action of trypsin and autolysis The disease is frequently associated with cholecystitis and cholelithiasis A calculus lodged in the papilla of Vater may dam up the bile until it is forced back into the pancreatic duct Cases reported by Opie and subsequently by many other observers have clearly demonstrated this In a series of patients at the

There are a certain number of cases that even at operation cannot be differentiated from carcinoma of the head of the pancreas For these cholecystogastrostomy or chole cystoduodenostomy is necessary Permanent relief and disappearance of jaundice are the therapeutic diagnostic tests

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PANCREATIC CALCULUS

Pancreatic calculi are rare and are usu ally found accidentally at autopsy Their presence is practically never recognized dur ing life They are usually small are com posed of calcium phosphate and calcium carbonate and in most cases are situated in the main pancreatic duct They are usually associated with chronic pancreatitis

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TUMORS OF THE PANCREAS

Gulecke s classification of pancreatic cysts is the most comprehensive He divides them into

Adenocystomata or cystic new growths which are multilocular as a rule and most often found in the tail of the pancreas

Rentention cysts the most common form which develop when the ducts are ob- structed and are usually associated with a chronic pancreatitis

Degeneration cysts which result from a softening and cystic degeneration of pan creatic tissue caused by necrosis or hemor rhage

Pseudocysts which are characteristically located outside the parenchyma of the pan creas and as a rule occupy the lesser sac These frequently form after injury to the pancreas and contain, at first changed blood later a clear glairy fluid composed largely of pancreatic juice

Symptoms and Diagnosis—Since Gussen bauer first diagnosed the condition in 1882 the symptomatology has been carefully studied but even today it is not clear cut Pain in the epigastrium or in the left upper quadrant the development of a palpable tumor in the region of the epigastrium or umbilicus and symptoms of indigestion simi lar to those of chronic pancreatitis are the common manifestations Because of the po sition of such cysts above the stomach or between the stomach and colon gastric and colonic inflation with air may aid diagnosis The x ray examination of the abdomen which has been inflated with a few hundred cubic centimeters of oxygen or sterile air may demonstrate the cyst A steadily en larging mass in the upper abdomen is the most characteristic sign

Treatment—Aspiration is a bad practice An exploratory incision under novocain an esthesia is desirable both to establish the diagnosis suggested by the other evidence and to evacuate the contents if the enlarge ment proves to be a cyst Suture of the open ing of the cyst to the abdominal incision (so called marsupialization) is then ad visable in order to prevent accumulation of fluid within the cyst

The use of sclerosing solutions such as sodium salicylate and quinine urea or even weak solutions of potassium hydrate may prove of great help in closure of the fistulae resulting from marsupialization of pancreatic cysts

Benign Tumors—*Adenoma of the Islet Tissue of the Pancreas Excision for Hyper insulinism*—The purpose of the operation is to remove single or multiple adenomas in tact with the least damage to the normal pancreatic tissue

After the diagnosis of chronic hypo glycemia is established and hepatic and pitu itary causes have been ruled out the patient should have a course of medical therapy of three to four weeks to determine the response of the individual to conservative measures If it is found that the blood sugar values are continuing to remain low and that seizures are controlled only on a high carbohydrate intake an exploratory celio tomy is indicated

CASE SELECTION—Patients in whom the diagnosis of hyperinsulinism is definitely made by excluding pituitary adrenal and hepatic etiology who have failed to re spond to medical therapy over a period of several weeks who continue to show low fasting blood sugar values and are becom ing obese because of the large amounts of sugar and carbohydrate required to control their hyperinsulinism should be operated upon

and of the released pancreatic ferments with the least trauma to the pancreatic tissue Some surgeons advise the breaking through of the capsule of the pancreas along its lower margin in order to provide for a release of tension If this can be done under vision it probably is wise to do so but in the major ity of cases the tissue is so edematous that *it is difficult to obtain a clear view of the* pancreas Therefore celiotomy with drain age of the involved portion of the pancreas and decompression of the bile ducts if jaun dice is present is the procedure of choice Modern methods of transfusion if followed by saline drip infusion can be carried on if necessary during and after the operation

Allen O Whipple

CHRONIC PANCREATITIS

The pathologic change characteristic of chronic pancreatitis is an increase in the interstitial connective tissue which replaces more or less of the parenchyma of the gland Opie has pointed out two histologic types of chronic inflammation (1) the interlobular usually associated with lymphangitis in which the increase of fibrous tissue is limited to the tissue between the lobes and (2) the interacinar in which the new growth of con nective tissue invades the interacinar spaces replacing the parenchyma and involving the islands of Langerhans In the interlobular variety, the lesion is more apt to be limited to a part of the pancreas especially to the head where it is most commonly associated with a descending infection of the biliary tract The interacinar type usually involves the entire gland and is frequently associated with diabetes mellitus

The increase in connective tissue may be caused by an arteriosclerotic or endarteritic condition of the vessels by a syphilitic proc ess or by blocking of the ducts Most often it is the result of long standing and per sistent infection of the lymphatics of the pancreas which communicate freely with those of the biliary tract duodenum and transverse colon

Symptoms and Diagnosis—Epigastric distress bloating and belching epigastric tenderness constipation or diarrhea and irregular jaundice are symptoms *common to* chronic pancreatitis They may also occur with lesions of the biliary system If how ever in addition the patient suffers from a sense of fulness and the stools are large foul and fatty, and contain undigested meat fibers or if there is sugar in the urine a diagnosis of chronic pancreatitis is probably correct The decrease or absence of pancre*atic ferments in the duodenal fluid* is added evidence The fluid should be obtained by the Einhorn tube and examined imme diately

Carcinoma of the pancreas is most dif ficult to differentiate from chronic pancrea titis Irregular jaundice a history of biliary colic and absence of an enlargement of the gallbladder suggest chronic pancreatitis while jaundice of gradual onset steadily in creasing without a history of biliary colic, and a palpable pear shaped gallbladder point to carcinoma of the head of the pan creas, or carcinoma of the papilla of Vater The newer technic of gastro intestinal fluoro scopy makes it possible to differentiate be tween *gastric carcinoma* and the chronic pancreatitis in spite of the similarity of symptoms The use of the duodenal tube to obtain duodenal *juice for* determination of pancreatic ferments may be of value in differentiating a carcinoma of the ducts from chronic pancreatitis and carcinoma of the pancreas

Treatment—For the interacinar type associated with glycosuria the usual medical measures employed in diabetes may be used Because of the digestive disturbances fats and proteins have to be largely eliminated from the diet Pancreatic extract is of real benefit in some cases, and may be given in doses of 0 3 to 0 6 Gm in salol coated capsules after *meals*

For the common interlobular type of pan creatitis the same treatment should be tried but surgery should be *employed to* remove any focus of infection such as chronic chole cystitis or biliary infection In many cases carefully watched at the Presbyterian Hos pital removal of the infected *gallbladder* or drainage of an infected common duct has resulted in permanent recovery from the symptoms referable to the diseased pan creas The results at the Mayo Foundation and at Lankenau clinic have for many years *proved the efficacy* of surgery in this disease

the lower end of the common duct can best be accomplished in early favorable cases in a one stage procedure The radical operation for these tumors of the ampullary region and pancreas based on the principle of wide *en bloc* removal of the tumors as required in modern cancer surgery, is evidently in an evolutionary stage Many more cases with five year survivals will be required before valid claims can be made for the operations as done at present But it must be remembered that these patients untreated have an average of six months survival from onset of symptoms until death Many of them are tortured with the uncontrollable itching of obstructive jaundice The considerable risk of 30 to 35 per cent is justified if they can be made comfortable even for a year or two If only these patients could be referred to the surgeon before they are studied to death while the cancer is small and localized and before the patients are seriously ill with weeks of obstructive jaundice a far lower operative mortality and a much longer survival would result

ALLEN O WHIPPLE

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DISEASES OF THE PERITONEUM

General Considerations —The peritoneum is the serous membrane which lines the walls of the abdominal cavity and is reflected to envelop the structures within the peritoneal cavity The portion of peritoneum which lines the walls of the abdominal cavity is called the parietal peritoneum and that which covers the viscera the visceral peritoneum In the male the peritoneal cavity is a closed sac but in the female the open ends of the fallopian tubes render peritoneal infection by that route possible

The reflections from the parietal peritoneum to the viscera are composed of two layers which form the mesentery omentum and peritoneal ligaments The peritoneum is composed of a layer of endothelium resting on a thin layer of connective tissue In the development of the embryo and rotation of the intestine the relations of the peritoneum become exceedingly complicated in that various compartments are formed all of which under normal conditions are in communication with one another but which in inflammatory processes may become separate compartments The two main compartments are the greater and the lesser and they are connected by the foramen of Winslow The main divisions of the greater sac are the right and left lumbar the central the pelvic and the subphrenic

In addition to surrounding and separating the viscera from one another and suspending them by various ligaments the peritoneum serves as a medium through which the blood lymph and nerve supply to these structures is carried The smoothness of the peritoneal surface and the fact that there is normally a small amount of fluid in the peritoneal cavity permit the movements of the viscera to take place with the greatest freedom

The defense mechanism of the peritoneum and the great absorptive power of this structure are in large part attributable to its enormous area which is approximately equal to that of the surface of the body The omentum is a large factor in protection against infection Its extent its close contact with the contents of the abdominal cavity its rich blood supply and its mobility give it the capacity to seal off localized infections or to become adherent to the parietal peritoneum and wall off large portions of the abdominal cavity The entire peritoneum possesses tremendous power of absorption and it has been shown that the rate and degree of absorption are the

END RESULTS —The author has operated on seven cases of hyperinsulinism six with excision of one or more adenomas of islet tissue as proved by pathologic examination the seventh with excision of four fifths of the pancreas These have all been followed for periods of one to three years All were cured of their hypoglycemia and 'insulin shock seizures One patient who had two adenomas and remained cured of his hyperinsulinism for twenty eight months was admitted to another hospital as an emergency and died of hemorrhage from a bleeding duodenal ulcer which developed a year after his operation for removal of islet tumors (For a review of all reported cases of hyperinsulinism up to 1938 see the article by Whipple in International Journal of Surgery 1938)

Benign cystadenoma of the pancreas is relatively rare and is often exceedingly difficult to differentiate from a retention cyst of the pancreas The relative amount of adenoma and cyst formation determines the pathologic findings

Malignant Tumors —Tumors of the pancreas are usually malignant and almost always carcinomatous Adenocarcinoma is the most frequent type Carcinoma usually occurs in the head of the organ and rapidly involves the common bile duct and adjacent lymph nodes

Symptoms —The symptoms vary with the location of the tumor but great weakness loss of weight and extreme anorexia are always present

If the tumor is in the head jaundice appears, as a rule gradually Unless the gall bladder has been previously inflamed it enlarges to an easily palpable pear shaped mass as the jaundice deepens There may be glycosuria but it is rare The presence of a palpable mass in the region of the pancreas is also very infrequent The pain and tenderness vary with the amount of involvement of the celiac plexus The pain is characteristically of a severe boring or grinding type and extends through to the back During the jaundice the stools are foul clay colored and fatty The blood clotting and bleeding times are prolonged as the jaundice deepens or persists

Diagnosis —As has already been stated differentiation between these tumors carcinoma of the papilla of Vater or carcinoma of the common duct and chronic pancreatitis, is almost impossible A persistent deepening jaundice coming on gradually without pain, in an elderly individual with a palpable gallbladder is almost certainly a sign of carcinoma of the head of the pancreas The use of the duodenal tube for a study of pancreatic ferments may help in the differential diagnosis of carcinoma of the common duct above the papilla and the other lesions

Treatment —In the late stages no treatment gives relief In the early stages the patient may be spared several weeks of great emaciation and pruritus by anastomosis between the gallbladder and stomach or duodenum In five patients seen by the writer a diagnosis of carcinoma of the head of the pancreas was made during operation all were relieved of symptoms for twelve to thirty six months by a cholecystenterostomy Cases that eventually prove to be chronic pancreatitis illustrate the difficulty of the differential diagnosis and the advantage of applying surgery to an otherwise incurable condition

Within the last few years progress has been made in the therapy of carcinoma of the papilla of Vater and early carcinoma of the head of the pancreas In 1938 the writer (Amer Jr of Surgery April 1938) published a new method of dealing with these lesions The operation is carried out in two stages in the first stage we ligate the common duct below the cystic duct and do an antecolic cholecystojejunostomy on the Roux principle of anastomosing the distal cut end of the jejunum to the fundus of the gallbladder with an end to side anastomosis of the proximal cut end of the jejunum to the side of the jejunum 10 to 12 cm below the cholecystojejunostomy

After three weeks the second stage should be done with first a gastrojejunostomy followed by an excision of the descending or second portion of the duodenum the ampulla of Vater with the lower end of the common duct and a wedge shaped portion of the head of the pancreas with ligation of the cut end of the pancreatic duct and closure of the pancreatic stump

More recently we have found that the radical removal of carcinoma of the head of the pancreas of the ampulla of Vater or of

While peritonitis due to colon bacilli is less fatal and fulminating than the other forms it is unfortunately usually a mixed infection and the other organisms frequently streptococci although not the primary invaders increase the seriousness of the infection to a marked degree

The streptococcus probably invades the peritoneum as frequently as the colon bacillus being introduced in the same manner as just mentioned although the most frequent sources are puerperal sepsis and 'infection introduced from without The exudate in such cases is thin watery slightly purulent odorless and contains no flakes of fibrin Peritonitis of this type is perhaps the most fatal and fulminating of all

The gonococcus may invade the peritoneum in the course of gonorrhea This is more common in females but may also occur in males Peritonitis in such cases is usually confined to the pelvis although on occasions it may be generalized The exudate is plastic and rapidly produces dense adhesions

The pneumococcus may be found in mixed infections but is also found in pure culture Pneumococcal peritonitis is usually observed in children between the ages of three and seven years although it has been known to affect adults also The condition in males is primary but in females secondary The pneumococcus in these cases invades the peritoneal cavity by way of the genital tract through the fallopian tubes and infection begins as pelvic peritonitis The exudate at first is thin watery and contains no flakes of fibrin within a few days however it becomes thick purulent and contains much fibrin This tends to cause adhesions and to localize the infection

Incidence—Little has been written on the relative frequency of acute peritonitis Some interesting figures were recently obtained by Pflaum however in the review of a series of 14 263 consecutive necropsies at the various hospitals in Minneapolis and St Paul from 1920 to 1932 There were 1000 cases (7 per cent) of general peritonitis in this group

The condition was considerably more frequent in females than in males and the greatest number of patients had been between the ages of twenty and thirty years The incidence in females reached its peak during this decade because the peak of gynecologic diseases occurs in this period Peritonitis was more frequent in males between the ages of forty and seventy years and perforated peptic ulcer and carcinoma were found to be the important causative factors The bacteriology was in accord with what has already been given

Peritonitis developed as a postoperative complication in 22 1 per cent of these cases and was attributed to appendicitis in 12 6 per cent to tuberculous infection in 10 per cent to abortion in 7 7 per cent to malignant tumor in 6 4 per cent and to perforating peptic ulcer in 4 8 per cent The lesions were also studied from the standpoint of mode of origin and 522 were found to have arisen from the alimentary tract 193 from the female reproductive organs and 88 from hematogenous infections The remainder were about equally distributed with respect to the source of infection

Morbid Anatomy.—The pathologic changes which occur in acute peritonitis are dependent on a large number of factors so that the course of peritonitis from a pathologic standpoint is by no means constant In massive infections resulting from rupture of a viscus or an abscess there is a prompt and general reaction which exhibits the characteristic changes seen in inflammation of any serous membrane The resistance of the peritoneum to certain types of infection is well known and certain types of organisms injected into the peritoneum of animals will produce little reaction The usual immediate changes which occur in the peritoneum are an increase of blood in the involved region and a gradual change from the normal glistening to a glazed appearance and exudation of plastic lymph of varying amount according to the nature and the extent of the infection The amount of fibrin which is formed also depends on the nature of the infection

In general the less serious the type of organism the greater the amount of fibrin and the greater the extent of the agglutination of the intestines the better the prognosis For instance in streptococcal peritonitis the amount of fibrin is small so there is little evidence of protective covering present A large quantity of thick pus within the abdo

same in all portions of the peritoneal cavity Some authors contend that absorption is more rapid from the diaphragmatic area than from the pelvic area, thus the basis for Fowler s position, but this contention is probably attributable to the fact that the lymphatics of the diaphragm are more easily *demonstrated than other peritoneal lymphatics* There is some controversy as to whether the lymphatics or the blood vessels are the main route of absorption There is no doubt that this process takes place through both, but the evidence suggests that the absorption from the blood vessels is greater

Much of the confusion in the classification of peritonitis results from an attempt to identify the different types according to the source of the infection (for example exo genous or endogenous) to its extent (for example local or general) to the course which it is pursuing (for example spreading or localizing) to the situation of the peritonitis (for example pelvic or central) or to the bacteria which are present (for example, *streptococci staphylococci, colon* bacilli or pneumococci) For practical pur poses, division of peritonitis into the acute and chronic forms is as satisfactory as any

DONALD C BALFOUR

ACUTE PERITONITIS

Etiology—Acute peritonitis may be at tributed to many causes and only the more important are listed here These may be divided into certain general groups of which the most common are

Infective Lesions—These may be situated in the appendix the pelvic organs of females the gallbladder or in diverticula of the colon they may be associated with acute diseases of the pancreas Rupture of an abscess or of pocketed secretions also gives rise to infec tive lesions

Noninfective Lesions—Aseptic peritonitis or noninfected inflammation of the perito neum occasionally is produced by mechan ical injury by irritation caused by antisep tics or by extravasation of blood urine bile pancreatic juice or the contents of cysts The diagnosis of aseptic peritonitis how ever, is never justified without surgical ex ploration

Acute Perforation of Lesions of the Gastro intestinal Tract—These lesions include chronic or acute ulcer, particularly of the stomach and duodenum, but also any ulcera tive process, benign or malignant, of the gastro intestinal tract for example typhoid ulcer, tuberculous ulcer and the lesions of chronic ulcerative colitis

Intestinal Obstruction—The intestinal obstruction may be either mechanical or paralytic Strangulated hernia paralytic ileus, intussusception volvulus mesenteric throm bosis malignancies and the like are frequent causes The rupture of intra abdomi nal organs by direct or indirect trauma either from crushing or penetrating injuries may produce peritonitis Peritonitis rarely results from rupture of solid organs except when extravasated blood becomes infected

Primary Peritonitis—This is compara tively rare usually fatal and most often seen in children

Postoperative Peritonitis—Peritonitis may occur after any intra abdominal pro cedure but it more frequently occurs fol lowing operations that involve opening of that part of the intestine in which the con tents are highly virulent as in the colon Peritonitis may also be caused by organisms introduced from without by faulty technic, by direct contamination from infective ma terial from the nose or throat of operating room personnel from soiling during the op eration from subsequent leakage from a suture line in the gastro intestinal tract or from rupture of a circumscribed accumula tion of infective material

Bacteriology—Although it is not possible to make a satisfactory classification of per itonitis on the basis of the causative bac teria it seems important to mention the organisms most frequently found in the per itoneal exudate These in order of frequency are *Bacillus coli* streptococcus staphylo coccus pneumococcus gonococcus *Bacillus pyocyaneus Clostridium welchii* and other anaerobes

Colon bacilli are usually introduced by rupture of an acute appendix or by per foration or rupture of some portion of the bowel The exudate is profuse purulent, flaked with fibrin and may have a fecal odor

Pain—The pain of peritonitis has no particular characteristics except that it is at first extremely severe when widespread contamination of the peritoneal cavity has taken place, such as occurs in perforated ulcer The pain is so acute in these cases that the patient gives every evidence of profound shock and of impending death He makes every effort to avoid moving and lies in bed in a position which will put the least strain on the abdominal muscles Shallow thoracic respirations limit movement within the abdomen as much as possible In the majority of cases pain remains localized as long as does the peritonitis One of the most deceptive features particularly that associated with an acute appendicitis is that there may be a quiescent period between that stage of infection and the beginning of a general peritonitis which may deceive the attending physician as to the true condition of affairs The mode of onset of the pain in peritonitis is not constant It begins suddenly when the abdominal infection is widespread but in many cases the process extends so slowly that at no time is there severe pain

Vomiting—Vomiting almost always occurs in some stage of general peritonitis It is characteristically of the nature of a regurgitation and as the process continues the vomitus is more and more like that of the secretions of the upper gastro intestinal tract although it has a fecal odor there are seldom any fecal particles visible This vomiting is evidence of more or less complete paralysis of the intestinal tract and it is a very ominous sign The vomitus is usually of small amount and is regurgitated frequently and without effort

In the early stage of peritonitis peristalsis is normal and hyperactive but as the process extends gradual paralysis of the intestinal tract takes place and in the later stages peristalsis is completely absent Other symptoms such as jaundice and increasing shock are evidences of the profound toxemia The blood picture usually reveals leukocytosis the cell count varying between 10 000 and 30 000 per cu mm One should be suspicious of the presence of some other lesion particularly pneumonia in those cases in which there is an extreme elevation Occasionally there may be but little change in the leukocyte count but a shift to the left in the Schilling count is present in these instances In general the leukocytosis is indicative of the degree of infection so that in the chronic forms of peritonitis for example, there may even be a leukopenia The urine contains albumin and casts as evidence of the toxemia present Blood cultures are usually negative

While this is a brief picture of a typical case of peritonitis there are many atypical cases The reverse of the picture is occasionally seen, chiefly in elderly people, in which there may be no symptoms at necropsy however a diffuse peritonitis may be found There may have been no pain whatever no distention no elevation of temperature and even no elevation in pulse rate until a few hours before death These atypical cases are usually encountered in patients who are markedly debilitated from some other disease particularly cancer and probably because of the low resistance, or the type of infection little reaction to the infection occurs

Between these two extremes the absence of certain symptoms may make the diagnosis of peritonitis difficult and even impossible until more definite signs develop Because of this and because the great majority of cases of fatal peritonitis are secondary to conditions which can be corrected by timely surgical intervention correct diagnosis of the primary condition is of paramount importance rather than any attempt to evaluate signs and symptoms which may be evidence of peritoneal involvement Acute appendicitis and perforated ulcer are the most important examples of this It is also true in cases in which direct or indirect trauma has given rise to evidence of some intra abdominal injury If there is delay until definite evidences of peritonitis are present it is usually too late to save the life of the patient whereas careful consideration of the significance of the signs and symptoms present in respect to the type of injury will force a decision as to whether or not an abdominal exploration is indicated in order to determine the extent and nature of the injuries

Differential Diagnosis—The more important conditions from which peritonitis must be distinguished are (1) pneumonia

men, such as is seen in infections by staphylococci or colon bacilli, is of much less serious import than a small quantity of thin serous fluid as is present in streptococcal infection

Except in the primary type of peritonitis the infection usually begins locally and if it does not extend beyond a certain area the inflammatory process subsides and the area of involvement is soon restored to normal The rapidity and completeness with which this local peritionitis resolves are remarkable If however the infection spreads and involves the general peritoneal cavity, it will in the majority of cases prove fatal the exceptions being those in which the bacteria or their toxins are not of the virulent type In those cases of general peritonitis in which recovery has occurred the capacity to absorb the products of the inflammation is evidenced by the fact that their complete disappearance may take place This capacity however, varies in different individuals and in some the ability to produce fibrin is so marked that adhesions of the widest extent and firmness remain The fluid exudate which always accompanies peritonitis of any extent tends to accumulate to a greater or lesser degree in the more dependent portions of the abdominal cavity namely the pelvis right and left flank and subphrenic region If the patient recovers a localized abscess may remain in one of these regions

The major intra abdominal findings at necropsy in cases of general peritonitis are the distention or matting together of intestinal coils and the peritoneal exudate This exudate varies in consistency color and amount depending on the amount of fibrin the types of organisms present and the source of the infection It may be hemorrhagic as in perforating wounds or malignant disease In some cases the infection may be so virulent as to cause death within twenty four or forty eight hours Under these circumstances little or no exudate may be present

Symptoms—The symptoms of acute peritonitis vary *considerably* both in character and degree and they are in a general way dependent on the extent and nature of the infection and the *resistance of the patient* Local peritonitis is a condition very commonly associated with inflammatory processes in the abdomen While the process remains *local* the symptoms if any are present, are indistinguishable even though they are not a constituent of this local process There may, however be local signs of such a peritonitis particularly in regional rigidity of the abdominal musculature It is when peritonitis becomes more general as it does in cases in which it is a blood borne infection and, therefore of the primary type, that its typical symptoms are displayed The cardinal symptoms in such cases are always present and the clinical picture of a patient with general peritonitis is when once seen never forgotten

Pain and vomiting are early symptoms Irritability of the intestinal tract may first be evidenced by hyperperistalsis later on by intestinal paresis Anxiety is a characteristic sign and the patient's appearance in the later stages was so vividly described by Hippocrates that the term Hippocratic facies is applied A sharp nose hollow eyes collapsed temples, the ears cold contracted and their lobes turned out the skin about the forehead being rough distended and parched the color of the whole facies being brown black livid or lead colored" The position in bed with the thighs flexed and the shallow thoracic respirations are also striking features Hiccups may be an early symptom The patient's mental alertness even to within a short time before death is almost pathognomonic Both the pulse rate and temperature are elevated although in some cases the latter shows very little elevation in the early stages, a continued rise in pulse rate and a falling blood pressure and cyanosis however are ominous signs. Sooner or later there are evidences of dehydration in the dry tongue and of extreme thirst Abdominal distention is usual and local abdominal tenderness is frequent muscular rigidity, particularly in the early stages of a fulminating peritonitis is in itself almost sufficient to make the diagnosis In cases in which peritonitis is due to perforation of a hollow viscus with resultant escape of fluid and air into the abdominal cavity the signs of free fluid and air may be elicited on examination The symptoms therefore of general peritonitis are such as rarely leave doubt as to the diagnosis

It is only when there are no signs of improvement or when there is increasing evidence of sepsis particularly in the development of chills a high temperature and leukocytosis that suspicion is aroused of a residual abscess When this abscess becomes of sufficient size a diagnosis can usually be made regardless of its situation Subphrenic accumulations are most important to recognize and in such cases the history is of great value since they usually occur after operations for appendicitis with localized abscess Roentgenologic examination and exploratory needling will usually determine whether or not an accumulation is present in this region

Treatment —Even more important than the early diagnosis and treatment of peritonitis is its *prophylaxis* This consists in the main of recognizing and caring adequately for lesions which if untreated often lead to peritonitis—lesions such as appendicitis pelvic infections of women especially those of gonococcic origin peptic ulcer intestinal obstruction cholecystitis and carcinoma The insurance of absolute surgical and obstetric asepsis is most important Campaigns against venereal diseases and the institution of centers of treatment are essential to the prevention of gonococcic peritonitis Avoidance of purgatives in the presence of abdominal pain is one of the chief prophylactic factors in peritonitis Preoperative treatment consists chiefly of rest starvation the withholding of narcotics and the avoidance of purgatives until a diagnosis has been made

At *operation* much can be accomplished in the prevention of peritonitis besides the removal of the focus responsible for the infection If there is any possibility of peritoneal soiling as in operations on the gastrointestinal tract the application of one of the sulfonamide compounds directly to the region of possible soiling often means the difference between peritonitis and an uneventful convalescence Both *sulfanilamide* 6 Gm (90 grains) and *sulfathiazole* 6 Gm (90 grains) have been used with good results The latter is felt by many to be superior because it is absorbed by the peritoneum less rapidly and therefore produces a high concentration of the drug locally for a longer time it also calls forth a more rapid and prolonged nonspecific peritoneal response of mononuclear phagocytes to deal with any organisms present Throckmorton has shown that sulfapyridine is irritating to the peritoneum and remains agglutinated thus calling forth a foreign body giant cell reaction which results in the formation of adhesions For these reasons it is less desirable for use locally on the peritoneum

Once peritonitis becomes established operation should be begun as soon as possible if the patient is in condition to stand a surgical procedure Of first importance is the removal of the focus (appendix ruptured peptic ulcer etc) which is responsible for the peritonitis Application of one of the sulfonamides (preferably sulfathiazole) to the region of contamination has proved very beneficial in many cases this has been supplemented by the administration of *sulfanilamide subcutaneously* (0 8 per cent solution) the initial dose for an adult is usually 400 to 500 cc subsequent doses are regulated by the concentration of the drug in the blood as a rule it is best to maintain a concentration of 5 to 8 mg per 100 cc *Supportive measures* are helpful As a rule nothing is given by mouth until the patient passes gas by rectum *Fluid balance* is maintained by intravenous administration of a 5 per cent solution of dextrose in distilled water and by the subcutaneous administration of physiologic solution of sodium chloride *Rest* in bed in the semisitting position is employed *Pain* is alleviated by repeated small doses of morphine *Transfusions* of blood or plasma are helpful especially if the patient is anemic or if the concentration of serum protein is low Distention is combated by gastric lavage or in more persistent cases by the indwelling nasal tube either the duodenal tube as advocated by Wangensteen or more recently the double lumen tube (Miller Abbott) which is connected to a constant source of suction The use of a rectal tube with glycerin suppositories enemas and the application of hot stupes to the abdomen may also help relieve the distention Pitressin eserine sulfate and acetylcholine are helpful in combating intestinal paralysis

DONALD C BALFOUR

and pleurisy, particularly in children, which must be distinguished from primary peritonitis, this is usually possible by careful examination if only one condition is present, (2) renal colic which is associated with spasm and rigidity of the abdominal muscles and evidences of shock, (3) intestinal obstruction, which is occasionally difficult to distinguish from peritonitis since they are so frequently associated that it is not always possible to determine which condition is primary, and (4) gallstone colic, in certain types of which there may be an associated rigidity of the abdominal muscles In all conditions in which there is muscular rigidity, this usually disappears or diminishes when morphine is given the rigidity associated with peritonitis on the other hand does not Various other intestinal conditions, such as intussusception volvulus or mesenteric thrombosis may in some cases be difficult to differentiate, although a carefully taken history will usually exclude them In addition any condition that may give rise to any of the symptoms which are present in peritoneal irritations may be confused with peritonitis for example ovarian cyst with twisted pedicle acute pancreatitis lead colic ruptured ectopic pregnancy coronary disease and the gastric crises of tabes

The most important occasions on which peritonitis can be recognized are when it is possible to save the life of the patient by dealing directly with the cause of the peritonitis The most common example of this is in perforated gastric or duodenal ulcer It is fortunate that in this disease the initial symptoms are so severe and so characteristic that it is relatively easy to recognize the condition and if the patient is operated on within a reasonable length of time after perforation recovery is almost the general rule

Prognosis.—The mortality of peritonitis is difficult to establish but it is certain that general peritonitis has by far the highest mortality of any acute intra abdominal disease If peritonitis is localized and remains so recovery is to be expected although a residual abscess is always possible Recovery when peritonitis has extended beyond the localized area is dependent on the virulence of the infection, the resistance of the patient and the power to localize the process The high mortality in peritonitis other than in exceptional cases is due therefore to the toxemia which results from absorption throughout such a large area and the little that can be done to prevent the process from spreading

The actual cause of death in peritonitis is usually considered to be bacterial toxemia resulting from direct absorption from the peritoneal cavity It seems probable however that there would be more recoveries from general peritonitis, and treatment would be more effective in dealing with toxemia if the condition were not so often associated with complications in themselves serious Chief of these complications are intestinal obstruction and pneumonia The frequency with which a pneumonic process of some degree is found in patients who have died of general peritonitis is very high and this is particularly true when peritonitis develops in debilitated patients Similarly the intestinal paresis almost constantly accompanying general peritonitis adds to the picture of intestinal obstruction If it were possible to eliminate this factor it would increase the possibility of recovery The power of the peritoneum and particularly of the omentum to wall off peritoneal infection is so remarkable that if no complicating factors were present recoveries would be more often seen than they are at present

Sequelae.—A special effort should be made to recognize the sequelae of peritonitis, whether local or general as they may be rather easily overlooked The most important of them in as far as intra abdominal conditions are concerned are residual abscesses and of these the most serious are those in the iliac fossa in the pelvis and in the subphrenic region These abscesses follow a varied course and may be gradually absorbed without any significant residua but more frequently unless drainage is instituted they rupture into adjacent structures particularly into the intestinal tract itself or into the general peritoneal cavity or through the abdominal wall

The general symptoms of a residual abscess may be entirely unobserved In the early stages the patient may have been very ill and possibly may have had a continuous high temperature and leukocytosis but no physical signs of an accumulation of pus

terminal picture of intra abdominal malig nant disease The chief diagnostic sign of carcinomatous peritonitis is the presence of blood in the exudate

The symptoms of chronic peritonitis are indefinite They depend to a large degree on the amount of ascites present and of in testinal disturbance by the adhesions In the majority of instances adhesions will exist without symptoms but they may give rise to obstructive symptoms or to some reflex disturbance There may be a recurrent colicky type of pain associated with nausea and vomiting Malaise slight fever consti pation and even a chronic intestinal ob struction might be present There may be ascites or palpable masses present

The treatment hould be surgical when there is a possibility of removing the causa tive factor Laparotomy should not be performed for adhesions unless there are symptoms of obstruction or some marked disturbance of function Much has been at tempted in the prophylaxis of postoperative adhesions This has consisted chiefly in the introduction of a foreign substance into the peritoneal cavity at the time of operation These foreign substances have consisted of various solutions such as amniotic fluid gases such as oxygen and nitrogen, oils and waxes such as olive oil and paraffin and membranes such as the amniotic membrane The results obtained have not been uni formly favorable The Elliott heat treatment of pelvic peritonitis in women has proved *beneficial*

Other than this treatment is sympto matic If enough ascites is present para cente is should be performed the diet regu lated and the patient instructed in the proper use of laxatives and enemas Relief of symptoms may be obtained in many instances by the institution of the simpler procedures the treatment of chronic perito nitis by any radical procedure is to be dis couraged

DONALD C BALFOUR

MALFORMATIONS AND TUMORS

Many malformations of the peritoneum have been observed but rarely are they of clinical significance Rotation of the gut may be interrupted at any phase in its evolution thus giving rise to various peritoneal *bands folds fossae* or *recesses* Lane s kinks an adhesive band stretching between the termi nal portion of ileum and the pelvic perito-neum and Jackson s membrane a peritoneal membrane spreading from the parietal per itoneum to the ascending colon are fre-quently mentioned In rare instances an *absence of the omentum* has been noted A bifid omentum and a third omentum have been reported The abnormal development of the fossae has led to the formation of *intraperitoneal hernia*

Tumors of the peritoneum can be divided into primary and secondary tumors The *en-dothelioma* is the most distinct tumor that originates in the peritoneal structure itself Its rarity justifies omission of further com ment

Secondary involvement of the peritoneum by growths developing in one of the adjacent viscera is frequent Metastatic lesions from carcinoma of any organ in the abdomen or elsewhere are not infrequent in the perito-neum They may occur by direct extension or result from dissemination or transmission through the blood stream

Pseudomyxoma peritonaei is one of the more interesting tumors which usually oc-curs by dissemination It is secondary to rupture of a pseudomucinous cyst of the ovary or of a mucous cyst of the appendix It is characterized by the formation of large gelatinous masses which are more or less *encapsulated and may penetrate any part of* the peritoneal cavity A very similar condi tion can be produced by colloid carcinoma anywhere in the digestive tract Surgical removal of this gelatinous material and the original growth have in some cases given a number of years of comfort Recurrence however is probable and the prognosis is bad

Lipomas fibromas and *sarcomas* (lipomas being by far the most frequent) are occa sionally found in the mesentery and omen tum They arise from the tissue between the peritoneal leaves and are usually connective tissue types of growth *Cysts* of the mesen tery and omentum are seen more frequently These are classified by Ewing as chylous cysts enteric cysts dermoid cysts and intra peritoneal cysts of nephrogenic origin There

PRIMARY PERITONITIS

Primary or idiopathic peritonitis is caused by the beta streptococcus and various types of pneumococcus It is comparatively rare and while it is occasionally seen in adults, the great majority of patients are children, usually girls, less than ten years of age The three modes of entrance of the organisms generally considered are (1) the blood stream, in disease of the respiratory tract, (2) the intestinal tract by penetration from the wall of the bowel, and (3) through the uterus and fallopian tubes in infection of the vagina The blood stream seems to be the most common pathway but the viewpoint of Cole, that there is probably more than one avenue of infection, is most logical The mortality figures are extremely high for both streptococcic and pneumococcic primary peritonitis Newell in a review of the literature reports an average mortality of 80 to 100 per cent in the former and 40 to 65 per cent in the latter group

Diagnosis is not easy because of the absence of a history of an intra abdominal lesion and because abdominal pain and vomiting are prominent features of many acute diseases among children Abdominal puncture is the most important aid in diagnosis and in a series of thirty cases reported by Pollock conclusive evidence of the underlying pathologic process was obtained in all

The treatment usually advised is drainage of the abdomen It is well accepted that this should be done where localization has occurred but some such as Horsley feel that drainage in the early acute stages may be harmful In view of our more recent experiences with serum and sulfonamide therapy, it is probable that early surgical exploration with bilateral drainage in both lower quadrants of the abdomen should be employed in the majority of instances of acute pneumococcic peritonitis

In pneumococcic peritonitis, sulfonamide therapy has appreciably bettered the results of the former treatment by serum it has the added advantages of less delay in starting treatment and is less expensive than serum therapy Sulfathiazole or sulfadiazine is the drug of choice The usual oral dose for an adult is 6 Gm (90 grains) the first day subsequent doses depend on the concentration of the drug in the blood the ideal concentration being 5 to 10 mg per 100 cc. The sulfonamides may also be given intravenously as a 5 per cent solution of the sodium salt. Sulfapyridine and sulfadiazine are probably best not used locally on the peritoneum Streptococcic peritonitis has shown a much less severe course since the introduction of sulfanilamide locally on the peritoneum and the oral use of sulfathiazole. Early laparotomy and drainage have proved to be of no value in the presence of streptococcic peritonitis Conservative treatment, with the early institution of sulfanilamide therapy, seems to offer most Other supportive measures, in the form of fluids administered intravenously and frequent small transfusions of blood should be instituted as indicated

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CHRONIC PERITONITIS

By far the most common form of chronic peritoneal inflammation is tuberculous peritonitis (see *Tuberculosis*)

Chronic peritonitis is usually regional and follows recovery from acute peritoneal infection Chronic pelvic peritonitis in women is one of the more common forms of the disease Postoperative adhesions are a manifestation of a previous peritonitis A serous or fibrous form of chronic peritonitis is usually described, but most frequently both varieties are present in a single case

Other forms of chronic peritonitis such as actinomycosis, Pick s syndrome (pericarditic pseudocirrhosis), in which both the parietal and visceral peritoneum are markedly thickened and white and chronic encapsulated peritonitis are rare This last named condition is described by Maingot as the formation of a membrane which envelops portions of the small intestine and mesentery together with resulting agglutination of coils of intestine These form globular tumors which may in some cases be demonstrable The patient usually complains of recurring attacks of pain There may be slight fever and a palpable mass The condition is considered to be the result of a peritoneal tuberculosis Carcinomatosis or carcinosis are terms applied to carcinomatous peritonitis—a condition which is frequently seen as the

minor procedure it has occasionally given rise to peritonitis or other serious complications Many operations have been devised for permanent drainage of the fluid The Talma Morison operation and other types of omentopexy have been beneficial in certain cases of cirrhosis

Chylous Ascites —Ascitic fluid most often is clear and has a yellow or greenish tinge It is alkaline and has a specific gravity from 1 008 to 1 015 The albumin content is lower than that of blood serum usually being about 2.5 to 4.5 per cent and there is little tendency to coagulation on standing When the ascitic fluid has an opalescent milklike appearance as a result of the presence of chyle it is called 'chylous' ascites This is a rare condition caused by obstruction or injury to the receptaculum chyli or the thoracic duct It is most often due to nephritis elephantiasis or malignancy

While pseudochylous ascites is also rare it is more common than chylous ascites It is caused by fatty degeneration of cells or chemicophysical change of a nonfatty nature in a serous ascites of long standing The two fluids can be differentiated by chemical and physical analysis

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are many retroperitoneal tumors which may secondarily involve the peritoneum One could include tumors arising from the supra renal glands kidneys, and pancreas in this group The chief retroperitoneal tumors are lipomas and sarcomas

Actinomycosis although never primary in the peritoneum, may arise secondarily and cause the formation of a tumor Echinococcus cysts may be formed in any part of the peritoneum, and they have frequently been the cause of an abdominal tumor of considerable size There are no characteristic symptoms by which the diagnosis of one of these rare conditions of the peritoneum can be recognized Many of them require no treat ment, but when treatment is necessary, it is usually surgical

DONALD C BALFOUR

ASCITES

Ascites is any collection of free fluid in the peritoneal cavity The term is usually used however, to describe a collection of a serous fluid Ascites is essentially a symptom and not a disease

Etiology—Ascites may be due to either local or general causes In the majority of cases, ascites is due to heart and kidney dis eases abdominal neoplasms cirrhosis of the liver, or tuberculous peritonitis Other forms of chronic peritonitis obstruction of the main portal vein or inferior vena cava by thrombosis enlarged lymph nodes or tumors of adjacent organs may also produce ascites Ascites is rarely seen in syphilis pernicious and aplastic anemia in the leukemias Hodgkin's disease splenomegaly associated with anemia, echinococcus disease, abscess and amyloid disease of the liver or pericarditic pseudocirrhosis of the liver (Pick s syn drome)

Symptoms—The patient will frequently mention that there has been a gradual in crease in the size of the abdomen with an associated sense of fulness and tightness There may be many general symptoms of which ascites is only a part The enlargement of the abdomen may be striking varying with the amount of fluid present There may be bulging of the flanks when the patient is recumbent or of the hypogastrium when he is upright The skin may be shining and tense and lineae albicantes may be present if the effusion is large The umbilicus may be flattened or everted The veins of the abdomen are often prominent especially around the umbilicus ('caput medusae")

When the fluid is free a fluid impulse may be obtained by striking one flank g ly and receiving the wave with the hand on the other flank A characteristic sensation of fluid displacement may be obtained by mak ing a quick dipping movement over the spleen or liver A shifting dulness on per cussion, present in the most dependent part, is the most valuable sign of ascites This is best elicited by careful percussion of the abdomen with the patient in various positions. An ordinary roentgenogram of the abdomen may occasionally be of assistance The with drawal of ascitic fluid is of course, a positive diagnosis, but at times a dry tap may be obtained owing to the presence of adhesions

Diagnosis—The diagnosis is based chiefly on examination of the abdomen and para centesis Ascites must be differentiated from all conditions which cause enlargement of the abdomen among which are gaseous distention ovarian cyst pregnancy distended bladder obesity and fluid hemoperitoneum. In a few cases in which the ascitic fluid is loculated by adhesions within the peritoneal cavity, it may be necessary to perform surgical exploration before a diagnosis can be made

Treatment—A patient having ascites *per se* should not be treated for an indefinite period without an understanding of the causative background Diagnostic laparotomy or peritoneoscopy as proposed by Ruddock and others may be necessary to establish this causative background When this has been established the treatment should be directed primarily toward the underlying cause which will be discussed in separate sections Certain general measures such as rest in bed limitation of the intake of fluid and a diet high in carbohydrates are beneficial Diuretic drugs such as ammonium chloride ammonium nitrate calcium chloride and certain organic mercury compounds are indicated in many instances The chief surgical procedure is removal of the ascitic fluid by a trocar (paracentesis abdominalis) While this is considered a

alone cannot differentiate between a sinus infection that is active and one that is clinically cured The history, the presence of a discharge in the nose the x ray plate and when possible irrigation of the suspected sinus may all be necessary to establish diagnosis

Treatment—Sinus infections are local manifestations of infection of the respiratory tract With the general therapy suitable for such an infection the local application of heat and the use of astringents in the nasal passages usually relieve the acute symptoms Nasal irrigations often cause aural infection and mastoiditis If the pain of acute sinusitis is very severe the patient should be referred to a rhinologist without delay because this usually precedes the onset of complications Chronic infections usually require special surgical treatment which favors better drainage

Infections of the Accessory Nasal Sinuses in Children—With the exception of the frontal sinuses the accessory nasal sinuses are well developed at an early age Sinusitis not infrequently complicates the exanthemata Children who are subject to recurring respiratory infections often have foci in one or more nasal sinuses Local treatment consisting of astringent and antiseptic nasal drops as well as gentle suction or irrigation will clear up many of the milder infections The removal of infected tonsils and adenoids is regularly indicated More rarely improved drainage by conservative surgery will be necessary It is of the utmost importance that any associated dietary deficiency or allergy be discovered and properly treated

Complications of Sinus Infection—Extension of the nasal infection to neighboring structures such as the eyes ears throat or tracheobronchial tree is commonly observed Alarming and often fatal intracranial invasion may also occur in the form of *meningitis cavernous sinus thrombosis epidural* or *frontal lobe abscess*

Osteomyelitis is a most important complication and may be precipitated by trauma or sinus surgery The fulminating variety is frequently followed by involvement of the meninges or brain by way of a widespread thrombophlebitis Edema of the soft tissues with characteristic doughy swelling is the outstanding clinical manifestation Radical removal well into the healthy surrounding bone is imperative in these cases

An orbital cellulitis or *abscess* may complicate an infection of the frontal or ethmoid sinuses especially in childhood Edema usually improves with conservative treatment but external drainage is indicated by the presence of exophthalmos with limitation of motion Needless infection of the orbital contents by premature incision must be carefully guarded against

Retrobulbar neuritis in the past has been frequently attributed to a posterior sinusitis because of rapid improvement following sinus surgery Accumulated evidence however has raised grave doubts concerning the frequency of this causal relationship Multiple sclerosis is the accepted cause of the majority of these disturbances and hasty surgical intervention is to be avoided

The frequent association of sinusitis with chronic diseases of the tracheobronchial tree—especially bronchiectasis as well as certain cases of asthma—has become well established Proper treatment of the nasal infection is imperative in these cases

Clyde A Heatly

TUMORS OF THE NOSE AND NASOPHARYNX

New growths starting in the nasal passages are not infrequent in children Fibroma and spindle-cell sarcoma are the common types The *nasopharyngeal fibroma* or *juvenile polyp* causes pressure necrosis of the bony structures and may invade the orbit or cranial cavity it occurs only in males between the ages of ten and twenty five years On account of the great vascularity of these tumors radium therapy gives the best results

In adults *sarcoma* is relatively rare in the nose but is common in the nasopharynx *Carcinomata* seldom cause obstruction because of early ulceration Sarcoma gives rise to large tumors and obstruction is one of the early symptoms of this type of growth

Enlargement of the cervical glands may be the first sign of a nasopharyngeal growth although obstruction to breathing a blood stained nasal discharge or ringing in the

DISEASES OF THE RESPIRATORY SYSTEM

DISEASES OF THE NOSE

UNDER normal conditions air is warmed, *moistened*, and cleansed during its passage through the nose The mucous membrane of the nose is continuous with that lining the accessory nasal *sinuses* and *is everywhere* rich in mucous glands If the nasal passages are obstructed by deflection of the septum, by hypertrophy of the mucous membrane of the turbinates or by enlarged adenoids, the mucous glands may be stimulated to increased activity and chronically produce a catarrhal discharge This catarrhal process may by spreading to the mucous membrane of the eustachian tube, *lead to changes in the middle* ear that result in impairment of hearing Obstruction of the nose favors pyogenic infection of the accessory nasal sinuses with such resulting symptoms as headache chronic discharge of purulent material much of which is swallowed and the general disorders associated with focal infection

Epistaxis is usually due to superficial ulceration of the anterior part of the septum *Hypertension however may* cause rupture of the vessels in the posterior part of the nose and profuse hemorrhage Hereditary multiple telangiectasis permits repeated hemorrhage that may lead to profound anemia The telangiectatic areas in the nose and nasopharynx bleed more easily than those on the mucous membranes of the mouth or tongue A blood stained nasal discharge in a child always suggests enlargement *and infection of the adenoids nasal* diphtheria the presence of foreign body, or congenital syphilis in adults it is frequently evidence of a new growth

CLYDE A HEATLY

INFECTIONS OF THE ACCESSORY NASAL SINUSES

Etiology—The most common cause of infection of the accessory *nasal sinuses is acute rhinitis Abscesses* at the roots of the upper bicuspid and molar teeth often rupture into the maxillary sinus and produce infection which *may give rise to no symptoms* other than a chronic unilateral nasal discharge Sinusitis may result from swimming or diving Trauma allergy and dietary deficiencies are important predisposing factors

Symptoms—The nasal communications of the accessory nasal sinuses are narrow and easily obstructed by the edema and discharge of thick mucus that accompany acute *inflammation This obstruction gives rise to* headache, which is the most characteristic symptom of acute sinusitis The mucous membrane of the nasal passages and accessory nasal sinuses is innervated by the trigeminus nerve, and the pain of sinus infection is most commonly referred to the area of distribution of this nerve Infection of the sphenoidal sinuses however may give rise to suboccipital discomfort

The headache or pain of sinus infection in contrast to that of hypertension intracranial growths neurasthenia and eye strain is usually limited to the face The pain of an acute infection of the frontal or maxillary sinus is usually localized over the affected sinus Chronic infection however particularly of the maxillary sinuses is *often* accompanied by discomfort over the forehead on the same side Infection of an ethmoidal *sinus usually causes* discomfort in the orbit or across the bridge of the nose Occasionally the pain of a sinus infection is referred to the mastoid region a fact explained by the innervation of the mucous membrane lining the mastoid cells by the trigeminus In acute sinusitis the pain may be constant, *but in the chronic condition* it is characteristically more severe in the forenoon and disappears toward evening

Diagnosis—Severe acute coryza or more general infection such as influenza or pneumonia is usually responsible for infection of an accessory nasal sinus From 15 to 40 per cent of *all infections* of the maxillary sinus are of dental origin X ray shadows

are so strikingly similar that a final diagnosis frequently depends on the results of this direct examination as well as on the cultures thereby made possible from the larynx itself The spasmodic form of acute laryngitis (*croup*) differs from the more common acute catarrhal inflammations in its characteristic nocturnal episodes of harsh metallic cough and often alarming inspiratory stridor and dyspnea which are relieved by steam inhalations and emetics and leave few residual symptoms the following day Acute infections of the larynx are so frequently complicated by varying degrees of obstruction that special consideration should be given to this difficult problem The picture of *obstructive laryngeal dyspnea* should be completely familiar to every physician for while the increase of dyspnea may be gradual the transition to terminal asphyxia and collapse in childhood may be alarmingly sudden The child is restless and anxious Respirations are rapid labored and accompanied by a harsh inspiratory stridor Pallor is more common than cyanosis The progress of the obstruction can best be followed by observing the degree of retraction about the thoracic cage for with progressing dyspnea increasing retraction is noted in the suprasternal notch the supraclavicular fossae the intercostal spaces and the epigastrium Cyanosis and apathy usually denote terminal exhaustion Atropine which thickens secretions and opiates which depress the respiratory center must never be administered to these dyspneic patients

Tracheotomy through the second or third tracheal rings should be carried out under local anesthesia in the presence of progressive and well established evidences of laryngeal obstruction This procedure not only insures a proper airway and puts the inflamed larynx at rest but also permits suction drainage of the profuse tracheal secretions which frequently complicate many of these cases and thereby constitute a continued source of danger from low obstruction (acute laryngotracheobronchitis)

Congenital laryngeal stridor is characterized by the onset of stridor shortly after birth The stridor is chiefly inspiratory is aggravated by crying and tends to diminish or disappear during nursing or sleep The voice sounds are unchanged and cyanosis is seldom observed This disturbance is caused by the vibrations of an elongated epiglottis as well as by the flabby structures of the upper rim of the larynx and gradually disappears with the normal growth of the larynx usually during the second year of life

Laryngismus Stridulus (*Laryngospasm*) —Laryngismus stridulous in children may be defined as a laryngeal stridor of sudden onset without fever It is rare during the first three months of life and most common in children from six months to two years of age Boys are more frequently affected than girls It is uncommon in breast fed infants and is nearly always associated with rickets The laryngeal spasm is a manifestation of the extreme irritability of the nervous system in tetany

Symptoms—An attack is characterized by the sudden onset of inspiratory dyspnea without premonitory symptoms Obstruction may be so marked as to cause temporary complete apnea with deepening cyanosis unconsciousness convulsions or death may follow in severe cases Usually however after fifteen or twenty seconds a characteristic deep inspiration shows that the glottic spasm has relaxed There may be numerous subsequent attacks The child may be normal between attacks or may show other evidences of tetany

Diagnosis—The age of the patient the absence of fever the periods of apnea followed by a characteristic crowing inspiration and the associated clinical signs of tetany (carpopedal spasm Chvostek s and Trousseau s signs etc) are pathognomonic Since a foreign body lodged in the larynx may however produce almost identical symptoms the larynx should be directly examined through a laryngoscope

Treatment—During the attack artificial respiration and cold applications to the face and chest are most effective Intubation and tracheotomy are rarely necessary Later the fundamental metabolic disturbances must be treated

Foreign Bodies in the Larynx—The sudden onset of paroxysms of coughing and dyspnea in a healthy child suggests the presence of a foreign body in the larynx trachea or bronchi Immediate tracheotomy may be necessary Metallic bodies such as coins may be localized with the fluoroscope Since less

ear may be the initial symptom Of 70 patients whose cases were reported from the Mayo Clinic only 38 had nasal symptoms Invasion of the pterygoid fossa with fixation of the jaw, pain or anesthesia in the area of distribution of the second or third division of the trigeminus, invasion of the orbit with paralysis of certain of the extraocular muscles or severe and constant headache from meningeal irritation are all common manifestations of malignant growth in the nasopharynx

Pyogenic infection of the accessory nasal sinuses is usually associated with all new growths arising in the nose Similarly infection of the ear commonly accompanies new growths arising in the nasopharynx

The removal of a piece of growth for microscopic examination may be necessary to establish diagnosis but encourages secondary infection which often leads to frequent and profuse hemorrhage

Treatment —On account of the anatomic relations, complete surgical removal of a malignant growth is seldom possible and irradiation is the most desirable therapeutic measure

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DISEASES OF THE LARYNX

INTRODUCTION

Stridor as a symptom may afford valuable clinical evidence as to the location of the lesion *Inspiratory stridor* is particularly common in children and suggests laryngeal diphtheria a foreign body, papilloma of the larynx, spasm or incoordination of the muscles of the glottis—as in laryngismus stridulus Almost any laryngeal irritation in a child may cause a glottic spasm the most frequent manifestation being the crowing inspiratory stridor of catarrhal laryngitis (croup) *Expiratory stridor* suggests an obstructive lesion in the trachea or bronchial tree This may be due to an inflammatory condition as tracheal diphtheria to asthma or pneumonia or to pressure from mediastinal tumors Aneurysm is the most common cause of expiratory stridor in adults, while pressure due to tuberculous glands is frequently provocative of this symptom in children It is important to emphasize that no patient with a marked stridor should be submitted to general anesthesia A patient with stridor is forced to use all his accessory respiratory muscles and a general anesthetic is liable to make the respirations cease abruptly

Early and frequent examinations of the larynx are important in the three following conditions (1) Pulmonary tuberculosis predisposes to catarrhal changes in the larynx tuberculous laryngitis is an important complication and if recognized in its early stage, may be cured by well-directed measures. (2) The recurrent laryngeal nerves are in close approximation to the posterior capsule of the thyroid gland and may be injured by pressure exerted by an enlarged thyroid as well as by operative procedures on this gland For this reason every patient with goiter should have a laryngeal examination both *before* and *after* operation The prognosis of an operative lesion of the recurrent laryngeal nerve is favorable provided the onset of the hoarseness is gradual and not immediate (3) Hoarseness when persisting in a patient over forty for more than three weeks is often due to cancer If recognized early the prognosis after operative removal and irradiation is good If however examination is postponed until the appearance of evident clinical symptoms of malignancy a cure rarely results from any method of treatment

CLYDE A HEATLY

COMMON LARYNGEAL DISORDERS IN CHILDREN

Acute Laryngitis —The larynx in infancy and childhood is characterized by its relative smallness its unusual irritability and its tendency to dangerous edema as the result of acute infections or instrumentation Direct laryngoscopy is essential to accurate diagnosis and is a most important advance over the inferential methods of former years The clinical manifestations of nondiphtheritic and diphtheritic infections

side is a common symptom of tuberculous laryngitis in the ulcerative stage

Treatment —The larynx of patients with pulmonary tuberculosis should always be examined at frequent intervals The onset of hoarseness demands immediate laryngoscopy and enforced silence The use of the electro cautery is generally recognized as the most important measure in local treatment It is used at white heat to avoid bleeding It is contraindicated in patients with high fever or very active pulmonary lesions Light ther apy as well as the local instillation of chaul moogra oil (20 per cent) has been employed for its palliative effects with varying success Dysphagia may often be relieved by injec tion of alcohol into the superior laryngeal nerve Tracheotomy is seldom indicated ex cept for stenosis or rapidly developing edema

Syphilitic Laryngitis —The gumma which is the common syphilitic lesion of the larynx is usually situated above the vocal cords on one side It is composed largely of dense fibrous tissue and unless it ulcer ates produces no symptoms other than hoarseness and slight stridor If ulceration takes place the resulting scar tissue usually causes marked deformity and stenosis of the larynx Laryngeal lesions associated with those of the mucous membrane of the pharynx in secondary syphilis may produce symptoms identical with those of acute catarrhal laryngitis Acute laryngitis which does not respond to treatment within a reasonable time should arouse suspicion of syphilis Simultaneous occurrence of both secondary and tertiary lesions in the throat is not uncommon

Diagnosis —The conditions to be differen tiated are *tuberculosis* and *new growths* The diagnosis depends largely on the evi dence of syphilis elsewhere in the body although it must be emphasized that tuber culosis and syphilis as well as cancer and syphilis are often associated

Treatment —Gumma of the larynx is very resistant to any general or local antisyph ilitic therapy and unless the local symp toms are urgent local laryngeal treatment is probably undesirable Injury to a gumma such as cauterization or excision of a piece for diagnosis encourages secondary infec tion and ulceration The secondary lesions in the throat and larynx are best treated intra venously

Benign and Malignant Tumors of the Larynx —**Benign Tumors** —The most common of the benign tumors in the larynx are the polyp and the papilloma The papilloma of the larynx in adults differs from that in children in that it is usually solitary and shows far less tendency to recur after removal, furthermore it is fre quently of tuberculous or syphilitic origin The symptoms of a laryngeal growth depend upon its location The long pedunculated polypi that grow on the vocal cords cause attacks of paroxysmal coughing and hoarse ness due to interference with accurate ap proximation of the vocal cords Benign growths seldom cause bleeding pain or dys phagia They are best treated by local ex cision through the mouth although local application of radium often causes complete disappearance of the more vascular type

Malignant Tumors —*Carcinoma* is al most the only malignant growth in the larynx in the trachea and bronchi sarcoma is common The point of origin of carcinoma is of considerable importance If it arises on a vocal cord the tumor is usually situated on the anterior half A tumor in this situa tion is termed intrinsic and is relatively benign If the growth involves the mucous membrane over the arytenoid cartilages or the lateral walls of the larynx above the vocal cords it is said to be an 'extrinsic growth and the prognosis is bad A carci noma that arises from the posterior wall of the larynx just above the opening of the esophagus is the most malignant of all laryngeal growths

Diagnosis —It is of the utmost impor tance to recognize carcinoma of the larynx early because only then can a cure be ef fected without recourse to radical mutilat ing surgery From 75 to 85 per cent of car cinomas of the larynx develop in males be tween the ages of forty and sixty The earliest symptom of a growth on a vocal cord is hoarseness when this appears in an individual forty years old or more it should be regarded as due to carcinoma until proved otherwise As differentiation of a malignant from a benign growth is often difficult at this early stage it may be neces sary to remove a piece of tissue for micro

opaque bodies, such as fish bones may not be demonstrable by the x ray, direct examination of the larynx and trachea is necessary In children all examinations should be conducted without anesthesia

Papilloma of the larynx in children, although benign has a mortality almost equal to that of carcinoma of the larynx in adults Fortunately, it is relatively rare, only twenty cases having been seen at the Johns Hopkins Hospital from 1912 to 1924 It may appear at any age and is much more common in boys

The exact *etiology* is uncertain, although experimental studies in Vienna suggest that an invisible, filtrable virus is the direct cause Both in structure and behavior the lesion resembles that of verruca vulgaris of the skin Even very slight trauma may cause implantation of new growths on the surrounding mucous membrane

Symptoms—The symptoms depend on the size and location of the tumor Slowly developing but progressive hoarseness, a paroxysmal cough and at a later period dyspnea, should excite suspicion of laryngeal growth

Diagnosis—Direct inspection of the larynx (without anesthesia) is necessary for positive diagnosis

Treatment—Simple removal of the tumor rarely results in cure but on the contrary usually stimulates further growth Repeated removal of the recurring growths and long continued general hygienic measures are required to cure this condition Early tracheotomy may be necessary The improved methods of fractional irradiation may prove helpful

CLYDE A HEATLY

COMMON LARYNGEAL DISORDERS OF ADULTS

Catarrhal Laryngitis—*Acute catarrhal laryngitis* is usually secondary to infection of the upper respiratory tract but may be brought on also by irritation from improper use of the voice as well as by excessive use of alcohol or tobacco or by chemical fumes The lesions in the larynx vary from slight subglottic hyperemia and edema to diffuse reddening of all the mucous membranes of the glottis and shallow ulceration Hoarseness is the most constant symptom but in the more acute condition there may be aphonia and a dry burning sensation in the throat Catarrhal laryngitis is differentiated from tuberculous laryngitis by the absence of pulmonary symptoms *true tuberculous laryngitis is always secondary to a pulmonary lesion* The *treatment* consists in abstinence from speaking with cold applications, benzoin inhalations regulation of the surroundings so that the air is moist and of even temperature, and rest

Chronic catarrhal laryngitis is due to long continued irritation from any of the causes of the acute condition The pathologic change which is usually most prominent in the posterior half of the larynx consists of thickening of the epithelium This condition was originally described by Virchow as *pachydermia* and is not to be confused with carcinoma The other lesions involve the vocal cords and the intrinsic muscles In the larynx as in the nose and nasopharynx, chronic irritation causes excessive secretion of thick glairy mucus which produces many of the symptoms of chronic laryngitis The cause of such chronic discharge from the upper air passages especially in pyorrhea chronic tonsillitis or sinusitis demands proper treatment Any excessive growth of epithelium between the posterior ends of the cords should be removed

Tuberculous laryngitis is always secondary to pulmonary disease The improved methods of diagnosis and treatment of pulmonary tuberculosis especially the increasing use of collapse therapy have greatly reduced the incidence of laryngeal complications Dworetzky reports an incidence of only 3 6 per cent in 500 cases in 1941 as compared with 25 6 per cent in a similar series in 1914 Wilson states that the incidence in minimal pulmonary disease is now less than 5 per cent and not more than 20 per cent in far advanced infections The earliest specific changes in the form of hyperemia and infiltration are usually localized in the posterior half of the larynx particularly in the interarytenoid sulcus Later changes include marked edema especially of the arytenoids or epiglottis ulceration of the vocal cords the formation of tuberculomas perichondritis or fibrosis Pain on swallowing often radiating to the ear on the same

pathogenic as for instance the pneumococcus

Etiology—Bronchitis is highly contagious and such bacteria as the streptococcus pneumococcus influenza bacillus *Micrococcus catarrhalis* and staphylococcus are commonly present in the bronchial secretions Whether or not these are the primary factors in the etiology of the disease has not been established It seems probable that a filtrable virus such as Dochez has demonstrated in connection with acute coryza is usually the initiating factor such a virus in the nose and throat presumably renders the bronchial mucosa susceptible to the secondary implantation of such organisms

Sporadic cases occur but it may be epidemic Not infrequently an entire household is affected many cases follow indoor crowding Chilling of the body seems to be a predisposing factor, perhaps by lowering body resistance but other factors including probably the specific virus must also be present It is most common in the spring and fall when the weather is changeable It predominates in very young children particularly under 3 years of age in the aged and in those greatly debilitated by other disease Some individuals seem to be especially predisposed to bronchitis and in them the slightest exposure may bring on an attack this may be due to some allergic factor In this connection it is recognized that the inhalation of dust will precipitate an attack in some persons

Acute bronchitis may occur as a feature of certain infectious diseases especially typhoid fever It also occurs as one of the manifestations of measles of whooping cough and of asthma The bronchitis of an asthmatic may be on an allergic basis and therefore a primary feature of the asthma or it may be the result of an intercurrent infectious agent Not infrequently an acute bronchitis is associated with hypertrophied tonsils and adenoids in children and often it is secondary to an infected sinus It may result from certain noninfectious agents as from the inhalation of poisonous gases or from the aspiration of irritant liquid or solid material

Morbid Anatomy—The involvement is usually bilateral although it may be more marked on one side than the other The mucous membrane is inflamed and covered with an exudate of sticky, grayish mucoid character sometimes mucopurulent and when influenza is associated hemorrhagic Patches of epithelial desquamation are observable but no ulceration The smaller tubes may be dilated The submucosa is usually edematous and infiltrated with leukocytes The mucous glands are swollen

Symptoms—The symptoms of this affection may come on abruptly but more frequently are preceded by the manifestations of an acute coryza or sore throat The larynx as indicated by hoarseness may be affected from the first When the trachea and bronchi become involved chilliness lassitude and soreness in the muscles of the back and extremities are usually the earliest complaints Later as the inflammation extends farther down the bronchi a sense of retrosternal soreness or tightness is felt A chill is rare but may occur at the onset in children Even in severe cases the temperature rarely exceeds 101° to 102° F and it commonly subsides within four or five days if it lasts longer than a week bronchopneumonia should be suspected The pulse is proportionately increased except in the influenzal cases The respiratory rate also increases with the temperature but if disproportionately increased some pulmonary complication must be suspected Cough develops almost at once and at first is dry rough and ringing After a day or two it becomes softer and productive of a scanty viscid material which is expelled with difficulty still later of a more profuse and mucopurulent or even purulent sputum The cough often persists for two to three weeks although the discomfort usually subsides with the fever

Physical Signs—No physical signs may be demonstrable over the chest this is particularly true as long as only the trachea and large bronchi are involved If however the medium sized bronchial tubes become affected rales may be heard bilaterally especially over the basis of the lungs posteriorly at first they are dry then moist and bubbling They may appear and disappear and change in their character and location frequently and are commonly associated with some roughness of the inspiratory and expiratory breath sounds When the signs are

scopic examination Extrinsic growths often ulcerate early, so that there may be bleeding and pain on swallowing The location of the earliest metastases of carcinoma of the larynx is in the deep cervical glands about the bifurcation of the common carotid artery

Tuberculosis syphilis cancer and *benign growths* may cause diagnostic confusion The age of the patient the appearance of the larynx and the result of general physical examination must all be taken into consideration before arriving at a final diagnosis Not infrequently a patient with cancer of the larynx is found to have a positive Wassermann reaction in such cases there is danger of continuing antiluetic treatment until the growth has become inoperable It is not unusual also to find both tuberculosis and carcinoma in a cervical gland removed for diagnosis

Treatment —Early removal of an *intrinsic carcinoma* and the affected cord results in a high percentage of cures In more advanced cases total laryngectomy is necessary *Extrinsic growths* are best managed by the improved methods of irradiation

Laryngeal Neuropathies —The muscles* that move the vocal cord are innervated by the recurrent laryngeal nerve a branch of the vagus This is frequently involved in pathologic processes and hoarseness results The common cause of *a recurrent nerve palsy* is an aneurysm of the arch of the aorta Other cases are a mediastinal growth tuberculosis of the apex of the right lung implicating the pleura dilatation of the left auricle as in mitral stenosis carcinoma of the esophagus and thyroid and metastasis and inflammation of the glands in the neck that involve the vagus Postdiphtheritic and syphilitic neuritis may also cause laryngeal palsies There are too so called *functional laryngeal palsies* which may be distinguished from the organic type by the sudden onset of complete aphonia without loss of ability to cough and laugh and by the movements of the vocal cords revealed by the laryngeal mirror

The recurrent nerve lies close to the posterior capsule of the thyroid gland and the onset of hoarseness following thyroidectomy indicates that it has been injured If the nerve is divided, hoarseness ensues immediately and may never entirely disappear If the hoarseness comes on gradually however it may be due to stretching or edema of the nerve, and the voice will ultimately return to normal If, during operation both nerves are injured but not divided inspiratory stridor develops suddenly because of inability of the cords to open during inspiration Temporary tracheotomy may be necessary

The *prognosis* for complete restoration of function following postdiphtheritic paralysis is good The laryngeal crises of tabes are really glottic spasms depending on syphilitic neuritis of the recurrent nerves For this condition also tracheotomy may become necessary since antiluetic therapy is not always effective

CLYDE A HEATLY

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* The cricothyroid a tensor muscle is supplied by the superior laryngeal nerve

DISEASES OF THE BRONCHI

BRONCHITIS

BRONCHITIS is strictly speaking an inflammation of the bronchial tubes Practically however the trachea is usually involved in the inflammatory process though the tracheitis may give rise to no additional symptoms or physical signs and requires as a rule no additional treatment The term tracheobronchitis is therefore more descriptive of the total pathologic process

Acute Bronchitis —Acute bronchitis may be primary and develop independently but usually it is secondary as when it follows or is associated with such conditions as an acute cold measles whooping cough or influenza It is of serious importance chiefly because of its most frequent complication pneumonia Acute bronchitis may serve to arouse a latent tuberculous infection of the lung or it may lower local resistance and so lead to infection of the lung by organisms frequently present but otherwise non

disease particularly when the maxillary sinuses are involved Not uncommonly it is associated with or secondary to some chronic pulmonary disease such as bronchiectasis interstitial pneumonia tuberculosis or pneumonoconiosis or the pulmonary congestion that results from cardiovascular disease Emphysema often dominates the clinical picture and asthma is frequent Gout and renal disease are said to be associated with some cases probably because of the coincident circulatory disturbance Aortic aneurysm and enlarged tracheobronchial lymph glands may be factors in its production Excessive smoking syphilis and alcoholism may be predisposing influences The long continued inhalation of inorganic dusts such as occur in stone cutters coal miners potters and grinders of metallic substances apparently gives rise to a primary form of the affection Chronic bronchitis usually occurs in older people mostly in males and in them it is commonly associated with bronchiectasis It is more common in winter and so is sometimes spoken of as the winter cough of the aged It may however occur in children especially in those who have hypertrophied tonsils and adenoids and in those with rickets or paranasal sinus disease

Morbid Anatomy—There is venous hyperemia of the bronchial mucosa with hypertrophy of the membrane in some instances and atrophy in others some longitudinal bands of elastic tissue may be visible and in places denudation of epithelium Ulceration is rare but atrophy of the muscular and glandular elements with eventual dilatation of the tubes often occurs Some chronic peribronchitis may be present causing thickening of the walls Emphysema is common The sputum is usually scanty but may be profuse it contains mucus epithelium and pus cells

Symptoms—The general health is little impaired fever is rare and pain is usually absent Cough is the outstanding symptom and it varies with the season of the year the time of day and the degree of physical activity It may occur only in the winter months at least it is more troublesome during that season Frequently it is worse at night or in the early morning and is exaggerated by physical exertion It may be periodic or paroxysmal and is usually relieved by expectoration of the bronchial secretions The sputum too is variable it may be scanty and very mucoid or quite profuse and mucopurulent or purulent, if it is offensive in odor bronchiectasis or abscess of the lung should be suspected When chronic pulmonary or cardiac disease is associated dyspnea on exertion is a prominent symptom when emphysema is present the shortness of breath is usually worse at night

Physical Signs—The physical signs of chronic bronchitis resemble those of the acute form consisting chiefly of moist rales of varying sizes throughout the chest additional signs due to associated conditions most often emphysema are frequently present The chest therefore is prone to be barrel shaped with hyperresonance and diminished expansion The cardiac apex beat is frequently not visible Dyspnea and cyanosis are common The rales are bilateral and generally distributed but most numerous at the posterior bases and usually coarse and of a sonorous or bubbling character When the bronchitis is in abeyance no rales may be audible The breath sounds may be feeble with a prolonged wheezy expiration

Diagnosis—As in the acute form care must be taken to eliminate other more serious conditions before accepting the diagnosis of chronic bronchitis Although pulmonary tuberculosis is not so frequently confused with this form as with acute bronchitis sputum examinations for tubercle bacilli should always be made Even in elderly patients not seriously ill with no special signs at the apices and no fever tuberculosis of the lungs will sometimes be discovered The character of the sputum and clubbing of the fingers will often serve to differentiate cases of bronchiectasis Roentgenologic study is always indicated and will not infrequently reveal bronchiectasis tuberculosis an unsuspected foreign body or advanced pneumoconiosis

Prognosis—The prognosis is hopeful in the young but beyond middle life few recover though they may never be seriously incapacitated by the disease Acute exacerbations are common and emphysema and bronchiectasis not infrequently result The mere presence of chronic bronchitis may be

confined to one side of the chest some other and more serious condition must be suspected

Diagnosis—The chief conditions to be considered in the differential diagnosis are pulmonary tuberculosis bronchopneumonia, asthma typhoid fever bronchiectasis measles and whooping cough In children the presence of foreign bodies in the bronchi and of mediastinal lymphadenitis must be given some thought The failure to remember that the symptoms and signs of these diseases frequently mimic those of simple acute bronchitis is responsible for most of the errors in diagnosis Many of these conditions can soon be recognized by the appearance of other signs and by the course of the disease If the cough lasts more than three or four weeks if the fever lasts more than a week and is of the afternoon type and if a loss of weight and malaise are associated tuberculosis must be suspected and roentgenologic studies made Bronchopneumonia as already indicated may be suggested by a disproportionate increase in the pulse and respiratory rates also by a sudden increase in the fever leukocytosis profound intoxication a preponderance of rales in one side of the chest or the development of additional and characteristic physical signs Radiologic and bronchoscopic studies may be necessary to eliminate such conditions as bronchiectasis or foreign body Whooping cough may not be distinguishable until the characteristic inspiratory whoop develops measles is usually recognized by its appearance in a child in the midst of an epidemic by the inflamed nasal and conjunctival membranes and by Koplik s spots

Prognosis—The prognosis of acute bronchitis as such is always good Because however of the frequency of bronchopneumonia as a complication particularly in young children and in elderly people caution in predicting the outcome is wise Serious consideration must be given to persons who have an arrested or quiescent tuberculous lesion

Treatment—Preventive measures are of great importance Children and all those who are especially susceptible should avoid contact with known cases of acute 'cold or bronchitis and exposure to cold without proper clothing to overheated and excessively dry indoor air and to indoor crowding Children with hypertrophied tonsils and adenoids should have them removed Infected persons should be isolated through the febrile stage of the disease and should have their sputum destroyed

Once the signs of the disease are manifest it is best to insist that the patient be put to bed in a well ventilated room and kept there until the fever has subsided. That is the most important part of the therapy it shortens the course of the disease and usually prevents complications Many patients are overtreated with drugs A thorough purge in the very beginning however and a mild sweat induced by a warm bath and hot drinks tend to shorten the course of the disease Fluids should be forced and only the simplest foods taken during the first day or two Dover s powder in small repeated doses (0 01–0 03 Gm) not only aids in the production of sweating but tends to relieve myalgia It acts more effectively if combined with small amounts of salol and acetophenetidin

Counterirritation over the anterior chest by means of a mustard plaster may help to liquefy the bronchial secretion Steam inhalations especially with benzoin also may accomplish this result but Hollinger considers that inhalations of 10 per cent CO in oxygen are even more effective The expectorant drugs such as ammonium chloride and terpin hydrate are said to help only in the liquefaction of the secretion of the main bronchi When the secondary infection is predominantly streptococcal pneumococcal or staphylococcal in nature the sulfonamides may bring about rapid improvement In the recurrent cases autogenous vaccines should be given a trial

If the patient lives in the city it is often helpful when the febrile stage has passed, for him to seek the seashore where he can be out of doors and in the sunshine This frequently cuts short the duration of the disease

Chronic Bronchitis — *Etiology* — The chronic form of bronchitis although associated with the same bacterial organisms as the acute variety rarely if ever develops from a single acute attack and it is doubtful if it often follows repeated acute attacks Seldom is it a primary affection It may be secondary to long continued paranasal sinus

volved in the morbid process thus constituting bronchopulmonary spirochetosis The specific bacteria were first demonstrated in bronchiectasis by Leyden and Jaffe in 1867 Their pathogenic significance was not realized however until 1905 when Castellani described two patients presenting symptoms suggestive of tuberculosis but in whose sputum the fusospirochetal organisms were found to be abundant For many years after that the disease was thought to be confined to the tropics Work in this country and France during the last few years however shows spirochetal infection of the bronchi and lungs to be surprisingly frequent.

Etiology—The disease is apparently quite contagious The causative organisms are frequently found in the mouth especially when advanced dental caries and pyorrhea alveolaris are present and they doubtless gain entrance to the bronchi from this source This may occur during inhalation anesthesia This spirochetes are apparently of several varieties The commonest type is thin and delicate with small uniform coils others are thick and long with irregular coils often one end is blunt while the other is pointed Chevalier Jackson has observed ulcers in the bronchi from which such spirochetes could be isolated

Morbid Anatomy—Superficial necrosis of the bronchial mucosa with early involvement of the elastic tissues results from the destructive action of the organisms As this tissue sloughs away deep ragged ulcers are left behind Blood vessels are eroded and bleeding occurs Dilatation of the bronchial wall eventually develops and unless their progress is arrested the organisms penetrate the adjacent lung Under such circumstances an abscess containing putrid necrotic material may develop and terminate in cavity formation or if the process is arrested in fibrosis Thus spirochetal bronchitis may lead to bronchiectasis lung abscess diffuse pneumonitis or gangrene Pleural effusion with the presence of spirochetes in the fluid has been reported

Symptoms and Signs—The disease may assume an acute or a chronic form When *acute* the onset is sudden with a chill and an irregular fever develops then cough and the expectoration of bloody and usually fetid material Fine diffuse rales suggestive of pneumonia may be present but the dyspnea is less The condition of the patient may improve within a few weeks but relapses frequently occur The *chronic* form sometimes follows the acute but may be insidious in onset and without fever Cough is present and usually is most severe in the morning, the sputum is abundant mucopurulent, often blood streaked and usually fetid Small hemoptyses may occur The course of the disease is often quite prolonged even for years A loss of weight and strength is common Tuberculosis is simulated not only by the symptoms but also by the physical signs The latter however are more often confined to the bases of the lungs especially to the right lower lobe Eventually one or more of the pulmonary complications may develop and terminate the case

Diagnosis—The diagnosis is made by the finding of large numbers of fusospirochetal organisms in the sputum Smears must be stained and examined immediately after collection since the organisms are quickly autolyzed Ordinary dyes do not stain them deeply so unless special stains are used great care must be taken in the microscopic examination Repeated examinations of the sputum are necessary in order to eliminate the presence of tubercle bacilli

The roentgenologic picture in chronic cases resembles that of tuberculosis and cannot be distinguished from it unless the lesions occur in the lower lobes In acute cases with lung involvement the roentgen ray shows a central shadow usually in the region of the hilum The shadow is not as definitely circumscribed as that of an ordinary lung abscess Rapid excavation with central cavity formation may be detected by repeated examinations There is seen also a tendency for multiple small cavities to form early with later coalescence into one large excavation

Prognosis—Death may occur with the development of some pulmonary complication Cure may be spontaneous but usually results from specific treatment

Treatment—Arsphenamine is specific in the treatment of spirochetal bronchitis and of bronchopulmonary fusospirochetal infection It is most frequently given as neoarsphenamine in intravenous doses of 0 6 Gm The symptoms physical signs and

indicative of a failing circulation with its serious possibilities

Treatment—The treatment resolves itself primarily into that of the underlying causative process whether that be chronic paranasal sinus infection, bronchiectasis rickets asthma, emphysema or other pulmonary disease or some cardiac condition Recurrent respiratory infections should be guarded against and the inhalation of harmful especially silicious dusts should be avoided Smoking should be stopped The general condition of the patient should be given special consideration and when possible residence in a mild equable climate is desirable, especially for elderly patients Much fresh air sunshine and nutritious food are indicated Rest is important and all strenuous physical exertion must be avoided The milder forms of exercise such as golfing are often beneficial

Drugs are of relatively little value in the condition and need be used only for special symptoms For the cough when excessive simple cough mixtures containing a little codeine or a bromide may be indicated in the paroxysmal cases potassium iodide is often of great value

Creosote in cases with putrid foul sputum is both bacteriostatic and deodorizing Autogenous vaccines deserve a trial in resistant cases and Jackson advises their use combined with bronchoscopic aspirations in the intractable purulent cases Holinger states that the expectorant drugs are helpful in liquefying the secretion in the first and second divisions of the bronchi but that to accomplish this result in the peripheral branches hyperemia and an increase in the rate and depth of the respirations is necessary These conditions he claims are best brought about by frequent inhalations of CO_2

Bronchiolitis Fibrosa Obliterans—This type of bronchitis originally described by Lange in 1901 is chiefly of pathologic interest although the clinical diagnosis has occasionally been made Landis believes that some of the cases diagnosed as acute miliary tuberculosis but which recover are instances of this disease and refers to one such patient of his who was alive and well after four years It is characterized anatomically by an ingrowth of connective tissue from the walls of the terminal bronchi with partial or complete occlusion of their lumina

The condition has followed the inhalation of poisonous fumes such as those of nitrogen tetroxide of lime and of chlorine it has developed secondarily to measles, whooping cough pneumonia and syphilis and to the aspiration of foreign bodies It would seem therefore that any inflammatory lesion of the finer bronchi may produce the occlusion

Pathologically in addition to the lesions incident to the primary condition there are numerous small grayish white nodules from 1 to 2 mm in diameter which resemble miliary tubercles but which may be differentiated with a magnifying lens by their angular form and on dissection by their location at the termination of bronchi Microscopically the small bronchioles are found partly or wholly obliterated by the connective tissue ingrowth Adjacent alveoli may be involved in the connective tissue process

The outstanding symptoms are intense dyspnea and cyanosis These disturbances are usually associated with the findings of diffuse fine crackling rales and some hyperresonance When such symptoms and signs follow the temporary subsidence of a bronchitis incident to the inhalation of poisonous fumes the diagnosis should be suspected It is usually missed when the condition is secondary to the inflammatory bronchial lesions of such diseases as measles and whooping cough Bronchopneumonia or acute miliary tuberculosis may come on in a similar manner and be impossible of differentiation The roentgenologic picture of the chest may simulate that of acute miliary tuberculosis

The *prognosis* in obliterative bronchitis is grave but recovery is possible

The *treatment* is symptomatic

Spirochetal Bronchitis—This special form of bronchitis is distinguished clinically from the other types by the presence in the sputum of large numbers of the so called fusospirochetal organisms' spirochetes and fusiform bacilli Other bacterial forms such as the vibrios and cocci may be associated but the fusospirochetes are believed to be chiefly responsible for the inflammatory lesion Not infrequently lung tissue is in

attacks The only characteristic observation is that of the expelled casts Landis refers to a curious flapping sound beginning in the middle of inspiration and extending to its end due to partially separated casts which may occasionally be recognized At times the respiratory murmur in the affected portion of the lung may be absent a case complicated by massive atelectasis has been described by Perlstein

Diagnosis—As already indicated the diagnosis must rest on the finding of the branching casts which can be accomplished most satisfactorily by floating the sputum in water It may be suspected when recurrent attacks of bronchitis with severe paroxysms of coughing and dyspnea occur Such attacks with abnormal physical signs limited to one base should always arouse suspicion of some condition other than simple bronchitis A foreign body or a tumor in the lung may give similar physical signs but in *these the cough and dyspnea are more persistent* and tend to grow worse steadily X ray and bronchoscopic examinations may be necessary to make the differentiation In asthma the signs are more diffuse and the dyspnea is expiratory

Prognosis—In the acute type recovery is usual although an occasional fatality from suffocation due to lodgment of a cast in the larynx has been reported The chronic form is less serious but recurrences take place even after intervals of years and emphysema may eventually result

Treatment—Potassium iodide in large doses is generally recommended Inhalations of creosote and intratracheal injections of medicated oils are sometimes used During the acute paroxysms it is wise to confine the patient to bed in a well ventilated room Circulatory stimulants such as camphor and caffeine are often indicated If suffocation is imminent bronchoscopy or tracheotomy may be life saving

T GRIER MILLER

BRONCHIECTASIS

Definition—Bronchiectasis is a chronic progressive disease of the bronchi or bronchioles characterized pathologically by dilatations of the tubes and an inflammatory reaction in their walls and clinically by chronic cough and the expectoration of large quantities of purulent sputum The dilatations may be congenital or acquired if congenital they are rarely if ever recognized clinically unless secondary infection occurs when the two types give rise to the same symptoms and signs Formerly regarded as rare bronchiectasis is now considered second only to tuberculosis among the chronic affections of the lung

Etiology—The congenital origin of bronchiectasis is supported by its similarity to perhaps identity with congenital cystic disease of the lung by its occasional association with other congenital anomalies (Kartagener) and by the frequency of atelectasis in infants In general however it may be said that two important factors operate to produce the disease first damage of the bronchial wall and second a mechanical influence The latter may act as a distending *force from within the bronchus or as traction* on the wall from without

The most frequent cause of damage to the bronchial wall is infection in the form of a *bronchitis* Long standing sinus disease especially maxillary sinusitis often precedes and is responsible for the bronchial infection The infectious material may be aspirated directly from the nasal cavities into the bronchi or transferred through the lymphatics or blood stream to the peribronchial glands and secondarily to the bronchial walls Other causes of bronchial infection leading to bronchiectasis are the infectious diseases of childhood especially whooping cough and measles Morse believes that in children an interstitial pneumonia is the most frequent cause Influenza by producing an acute widespread peribronchiolar inflammation is an important etiologic agent Other causes of bronchial damage are the inhalation of irritating fumes with resultant sloughing of the bronchial mucosa and softening of the underlying structures the inhalation of inorganic particles such as coal and silicious dusts and the aspiration of foreign bodies

In spite of such damage a bronchial wall will rarely dilate abnormally unless it is subjected to unusual pressure from within or traction from without Relative increase in intrabronchial pressure sufficient to act a

roentgenologic evidence in early cases without fibrosis begin to disappear after the first dose and often recovery takes place after four or five injections Although anatomic cure cannot be obtained in advanced cases with extensive destruction of the lung arsphenamine will often arrest the process and thereby allay the symptoms of activity

Fibrinous Bronchitis —Fibrinous bronchitis also referred to as plastic croupous or pseudomembranous bronchitis is a rare disease characterized by the expulsion of casts which tend to assume the shape of bronchial tubes

Etiology—The cause of fibrinous bronchitis is not known Walker looks upon it as closely allied to bronchitis bronchiectasis and asthmatic bronchitis and states that often there is a previous history of some infectious disease or of a chronic bronchitis Engel believes that a local metabolic disturbance in the bronchi is responsible and compares it to the production of mucous casts in membranous colitis Some claim that a special precipitating ferment mucinase is secreted and can be identified in the serum of patients suffering from the disease Similar casts sometimes occur in laryngeal diphtheria obviously due to the diphtheria bacillus but it is customary to classify these separately In lobar pneumonia tuberculosis measles and scarlet fever also in certain heart affections bronchial casts occasionally develop but these being purely symptomatic are excluded from the so called idiopathic type of fibrinous bronchitis

Morbid Anatomy—Fibrinous bronchitis seems to begin as a simple bronchitis with tenacious fibrinous or mucoid secretion which eventually leads to the formation of casts that fill the bronchi and bronchioles Usually only portions of the lower lobes of the lungs are involved and sometimes but one side of the chest The medium sized tubes are involved first with extension into the bronchioles The bronchial mucosa in the affected areas may show desquamation of its epithelium ulceration or even caseous infiltration The casts themselves are gray white or pinkish in color fairly firm and often several inches in length When expelled from the bronchi they can be floated in water The branches correspond to the divisions of the bronchial tree The larger ones are often hollow and have a laminated appearance due to successive fibrinous or mucous deposits, the smaller ones are solid and terminate in spirals At times they are composed entirely of fibrin again of mucus and still again of the two combined in varying proportions Some blood streaking may be present

Symptoms—Acute and chronic forms of the disease are recognized The *acute form* may begin with a chill fever pain in the chest cough and dyspnea or it may come on with the symptoms of an acute bronchitis Commonly a moderate leukocytosis occurs and some cases show an eosinophilia As the casts form the cough becomes tight and paroxysmal loosening up as the casts are expelled Likewise with the formation of the casts and until they are coughed up an oppressive suffocative type of breathing is present Such cases are usually diagnosed only when the casts are found sometimes by the patient sometimes accidentally by the physician on examination of the sputum They may appear alone or as a pellet surrounded by sputum With them in the sputum may be found Charcot Leyden crystals or Curschmann spirals and eosinophils thus suggesting a condition similar to bronchial asthma The attacks may continue for a few days to several weeks and end in recovery or occasionally in the more severe cases death may result from suffocation

The *chronic form* may develop from an acute attack and commonly manifests itself by recurrent mild paroxysms of the acute type over periods of years The intervals of freedom may be of fixed duration as when the attacks occur at the onset of menstruation or they may be totally irregular and quite long Often in an individual case the casts are of constant size and come from the same bronchial area The clinical picture in the paroxysmal attacks is the same as for the acute variety except that fever rarely occurs The general nutritional state of the patient is not usually affected Emphysema may result and sometimes epistaxis and hemoptysis occur

Physical Examination—The physical signs may be those of an acute or chronic bronchitis or they may be normal Dyspnea and cyanosis may be present in the acute

Desquamation of the epithelial cells frequently occurs early exposing vessels from which hemorrhage may ocur The cilia of the lining cells are usually lost permitting stagnation of fluid and the accumulation of a purulent secretion in the cavities In certain cases known as dry bronchiectasis this secretion is minimal Cultures from material contained within the cavities show a wide variety of organisms

The bronchiectatic cavity may be differentiated from one due to tuberculosis by its smooth walls and by the points of entrance and exit of the involved bronchial tube, furthermore the contained secretion is more often fetid

The surrounding lung tissue may be involved in the morbid process if there is ulceration and destruction of the bronchial wall and fibrosis abscess or gangrene of the lung may ensue When fibrosis is extensive compensatory displacement of the lung and mediastinal structures toward the affected side may be present as well as scattered areas of compensatory emphysema The heart may present evidence of damage as a result of the increased resistance to the pulmonary circulation Pericarditis suppurative pleuritis pneumonia amyloid disease and even intracranial abscess may occur as terminal complications

Symptoms—Early in the disease the symptoms are not distinctive and are often attributed to associated conditions Cough is the chief early symptom and it usually follows an acute respiratory infection The cough may disappear to return however each time the patient contracts a cold or other mild respiratory infection Frequently the only other symptom present at this time is a sensation of lassitude As the disease progresses the cough becomes chronic In a well established case it is characteristically paroxysmal and is brought on by changes in the patient s posture For this reason it is usually most severe in the morning upon arising and at night upon lying down The cough leads in a typical case to the expectoration of large quantities of frothy sputum but the amount may vary from a few cubic centimeters to a liter a day Changes in posture of the patient may greatly influence the amount of sputum and the ease with which it is brought up It is sometimes foul smelling but this feature is by no means as common as was formerly believed Characteristically it settles on standing into three layers an upper frothy layer an intermediate one of thin turbid greenish fluid and a lower heavy one composed of pus cellular debris bacteria fatty acids and hematoidin crystals Hemoptysis occurs in about 50 per cent of the cases and is often copious Recurring respiratory infection of all types is the rule In spite of the chronic cough the patient maintains an appearance of fair health is usually afebrile and does not lose weight until the disease becomes extensive and involves a large proportion of the lung parenchyma Fever and chills may occur with the involvement of new areas of lung tissue and finally late in the disease when a large part of the lung is involved dyspnea cyanosis and pain develop Hemorrhage may occur and in the dry hemorrhagic type it may be the only symptom When the disease begins in childhood the manifestations are somewhat different No sputum is expectorated because of the habit of swallowing it A slight rise in temperature is frequent and because of recurring respiratory infection the child fails to gain weight as he should

Physical Signs—In the early stages of bronchiectasis the physical signs are often obscured by those of the associated bronchial or pulmonary disease chronic bronchitis atelectasis pneumonia emphysema or diffuse pulmonary fibrosis This is especially true when bronchiectasis coexists with tuberculosis In some early cases the physical examination of the chest is entirely negative in others the only positive sign may be the presence of a few rales over a small area usually at the base of one lung On the whole the quality of the physical signs is less important diagnostically than their location Many errors in diagnosis will be avoided if it is remembered how seldom an early tuberculous lesion is found in the lower lobes and how frequently bronchiectasis begins in these areas

As the process develops the signs change and may be very confusing If it is unilateral the breath sounds are usually suppressed and some lagging of the affected side of the chest during inspiration may be observed The mediastinal structures are frequently

a dilating force occurs in various conditions Hedblom has shown that normally with each deep inspiration a difference of about 10 to 20 cm of water exists between the negative intrapleural pressure and the positive atmospheric pressure in the bronchi this constituting the normal distending force within the bronchi Such a force is not sufficient to distend unduly a normal bronchus but it may be sufficient to cause dilatation of one previously injured by infection Any factor, however, which increases the normal disparity between intrabronchial and intrapleural pressure will tend to dilate the bronchi abnormally Such a condition exists when pulmonary atelectasis occurs Because the collapsed lung is unable to expand with the chest wall an increase in the intrapleural space and therefore, an increase in the negative intrapleural pressure occurs This results in an increased difference between the intrapleural pressure and the intrabronchial atmospheric pressure In some cases this difference is said to equal 45 cm of water *Atelectasis* therefore is one of the important causes of bronchiectasis some of the most marked cases of bronchiectasis are seen as a result of this condition Atelectasis itself is most often due to bronchial obstruction and in consequence bronchial obstruction is regarded as the chief cause of bronchiectasis Within twenty four hours after bronchial obstruction atelectasis of the corresponding lung may occur, and bronchial dilatations may be present within a few weeks The lodgment of a foreign body in a bronchus cicatricial stenosis or extramural pressure may be responsible for bronchial obstruction and thus be the ultimate cause of bronchiectasis Fibroid tuberculosis pneumoconiosis unresolved lobar pneumonia repeated bronchopneumonia and lung abscess also tend to reduce lung volume and so bring about bronchiectasis by the same mechanism as atelectasis Bronchiectasis itself produces fibrosis of the adjacent lung tissue and once established tends to perpetuate itself

Cough was at one time thought to be a cause of increased intrabronchial pressure and therefore important in producing bronchiectasis It is true that while the glottis is closed during cough there is some elevation of pressure within the bronchi At this same instant, however sufficient external pressure is exerted throughout the chest by the chest wall and abdominal muscles to counterbalance this increase Cough therefore, unless a bronchus is obstructed is probably not important mechanically in producing bronchiectasis If however, an obstruction is present, cough may increase the intrabronchial pressure beyond the obstructed area Cough also may be important in the etiology of bronchiectasis because it spreads infective material from one bronchus to another this has been observed under the fluoroscope after the instillation of iodized oil

Traction from without the bronchial wall is the other mechanical force operative in some cases of bronchiectasis It occurs in such a condition as adhesive pleurisy, in which during each inspiration this force is exerted Likewise, fibrosis within the lung sometimes so distorts the lung structure that a direct pull is put upon certain bronchial walls during inspiration Under such circumstances the bronchial wall if weakened by infection may yield by dilatation In abscess of the lung also, the factor of traction may be present

Occasionally bronchiectasis is observed without any sign or history of other respiratory infection It is believed that in such instances there may be a primary infection in the bronchus which produces bronchiectasis The sputum in such cases is green unusually foul smelling and shows large numbers of fusospirochetes which are believed to be the etiologic agents

Morbid Anatomy—The bronchial dilatations may be cylindrical saccular or fusiform and vary in size from a few millimeters to several centimeters in diameters They involve either the bronchi or bronchioles or both The upper lobes are rarely the seat of these lesions except when tuberculosis is the cause of the disease The most frequent sites of early involvement are in the lower lobes in the vicinity of the costophrenic and cardiophrenic angles In at least half of the cases the lesions are unilateral The pathologic changes in the bronchial wall depend upon the stage of the disease and vary from almost none in very mild cases to complete destruction of the entire wall with replacement by fibrous tissue in severe cases

come in most cases Churchill in a series of 122 carefully selected cases—some bilateral—had a mortality of only 3 3 per cent, Edwards in 166 lobectomies of only 3 7 per cent (none in fifty four consecutive cases) Johnson has had no deaths in six total pneumonectomies and six lobectomies

Treatment —Prophylaxis is most important This resolves itself into the proper care of all patients suffering from acute or chronic upper respiratory tract infection especially sinusitis the prompt and thorough treatment of all fusospirochetal affections of the mouth careful measures to rid the nose tion no matter what the cause and to manage properly all other recognized pulmonary diseases such as chronic bronchitis lung abscess pneumoconiosis asthma etc At the same time measures designed to improve the patient s general condition are strongly indicated Rest sufficient sleep fresh air and good nutritious food are essential

Special therapeutic measures include the use of antiseptic nasal sprays and mouth washes to prevent irritation and secondary infection from the septic discharges and various procedures to increase drainage from the bronchial cavities Posture may be of



Fig 83



Fig 84

Fig 83 —Bronchiectasis involving both lower lobes Note the irregular mottled densities in both lower lobes, flattening of the domes of the diaphragm and hyperventilation of the upper lung fields (Courtesy of Dr E P Pendergrass)

Fig 84 —Same case as Figure 83 Instillation of lipiodol reveals the dilatation and sacculations characteristic of bronchiectasis (Courtesy of Dr E P Pendergrass)

throat and mouth of infection before general anesthesia and the use of all known precautions against the aspiration of foreign material during operations and the prompt removal by the bronchoscope of foreign bodies in the trachea or bronchi Similarly the proper treatment of all bronchial and pulmonary infections must be regarded as a prophylactic measure against bronchiectasis When once the diagnosis of bronchiectasis is made the first obligation of the physician is to treat adequately the suspected causative factors to eradicate foci of infection in the upper respiratory tract and mouth to overcome demonstrated bronchial obstruc the greatest aid in evacuating the bronchiectatic cavities and involves keeping the head and shoulders well below the level of the pelvis for periods of a half hour several times daily This may be accomplished by hanging the head over the edge of the bed until it touches the floor bending the body sharply over a chair or markedly elevating the foot of the bed while using no pillows The inhalation of benzoin or creosote vapor is frequently quite soothing to the irritated throat and bronchial membranes Arsphenamine intravenously is of undoubted value in the cases due to spirochetal infection

The sulfonamides are helpful in many

displaced toward the affected side When the disease is bilateral the signs are often confused with those of a preexisting bronchitis If the lesions are superficially located some hyperresonance or even tympany may be demonstrable on percussion but if deep-seated even fair sized cavities may fail to influence the percussion note Sometimes an area that is dull to percussion may become hyperresonant immediately after a paroxysm of coughing which empties the cavity The distinctive signs of cavity formation—cavernous breathing bronchophony and pectoriloquy—are unusual but may be marked At times a peculiar soft sound suggesting the entrance of air into a small cavity may be heard at the end of inspiration this is known as Skoda s veiled puff

Clubbing of the fingers and toes is more marked in bronchiectasis than in any other pulmonary disease and is consequently of decided diagnostic value These phalangeal changes are particularly common when the lower lobes of the lungs are involved and when suppuration is extensive

In children the physical examination according to Landis is usually negative and the diagnosis depends almost entirely upon the roentgenologic picture

Diagnosis —Early in the disease both symptoms and physical findings are inconclusive and so recourse to special diagnostic procedure is indicated whenever any suspicion of bronchiectasis is aroused Even late in the disease when the symptoms are entirely characteristic the exact location of the lesions is often impossible without the aid of special examinations The first of these is a roentgenologic study of the chest Not always however can the diagnosis of bronchiectasis be made positively from simple x ray investigation The only positive observations from such a study may be some exaggeration of the linear markings of the lungs and when the lung tissue itself is involved a few scattered areas of density in the pulmonary areas These changes while consistent with a diagnosis of bronchiectasis may be simulated by a diffuse bronchitis or by tuberculosis Such study does serve however to eliminate certain other pulmonary conditions and often justifies further investigation regarding bronchiectasis

To arrive at a conclusive diagnosis and to locate the bronchiectatic lesions accurately some opaque medium must be introduced into the bronchial tree The material most widely used for this purpose is iodized oil Its value is greatest when a bronchoscope is used first to remove secretion from the portion of the lung into which the lipiodol is to be introduced Then by means of a catheter previously inserted, the lipiodol should be injected while the patient is under a fluoroscope It can be seen to enter and fill out any bronchiectatic cavities present thus definitely localizing them and establishing the diagnosis It is safer not to use iodized oil when the vital capacity is reduced to 50 per cent, or in the presence of an active tuberculosis hyperthyroidism or iodine hypersensitiveness Bronchoscopy is also an important aid in the diagnosis and should be performed in certain cases in order to eliminate as the cause of disease a foreign body or some other bronchial obstruction Marked clubbing of the fingers is an important diagnostic sign

Smears of the sputum should be examined to eliminate the presence of tubercle bacilli and more rarely the sulfur granules of actinomycosis Special search should be made for the presence of fusospirochetes, since their presence in large numbers indicates a special type of therapy

Because bronchiectasis rarely occurs without other pathology in the bronchi and lungs the chief problem in differential diagnosis is to distinguish between such diseases as chronic bronchitis pulmonary tuberculosis lung abscess unresolved pneumonia and asthma accompanied by bronchiectasis and those same diseases without bronchiectasis This must depend chiefly upon the special diagnostic procedures just mentioned

Prognosis —Bronchiectasis is a progressive disease but if treated effectively in the early stages the chances of complete recovery are fair Later however the process becomes irreversible and unless the involved area is excised leads to chronic invalidism or death from some of the complications Perry and King found that 26 per cent of a non operated series died within five years and that only 0 4 per cent of those who developed the disease in the first decade of life lived to forty On the other hand modern surgical interference offers a favorable out

chills sweats and loss of weight, indicative of chronic pulmonary infection When the foreign body is obstructive to a bronchus the symptoms soon become those of atelectasis or pulmonary abscess

Physical Signs —Jackson has described three pathognomonic signs to indicate the presence of a foreign body in the trachea (1) the audible slap caused by the sudden arrest of the foreign body as it is coughed up against the subglottic narrowing (2) the palpatory thud the sensation transmitted by this arrest to the examiner s finger as it is held over the cricoid cartilage or trachea and (3) the asthmatoid wheeze heard by placing the bell of a stethoscope at the patient s open mouth

With the presence of a nonobstructive foreign body in a bronchus there may be no abnormal physical signs sometimes harshness of breath sounds with an expiratory wheeze and coarse bubbling rales indicative of a localized bronchitis may be audible over the affected area If the obstruction is complete atelectasis with diminished chest expansion on the affected side results and an impairment of resonance with decreased or absent breath sounds may be recognized some displacement of the heart and mediastinal structures to the affected side may be demonstrated At times the foreign body acts as a ball valve allowing the entrance but not the free exit of air under such circumstances a localized emphysema results with displacement of the heart to the opposite side Eventually the signs of pulmonary abscess including clubbed finger ends and curved nails as well as foul and bloody sputum may develop Confusion is not infrequently caused by the presence of auscultatory signs on the nonaffected side these may be due to actual extension of the inflammation or to the shifting of secretions or of the foreign body itself to the other side



Fig 85



Fig 86

Fig 85—Foreign body (peanut) in the left main bronchus producing massive atelectasis and drowned lung In the inspiratory phase the mediastinum is displaced toward the affected side (Courtesy of Dr E P Pendergrass)

Fig 86—Same case as Figure 85 In expiration the mediastinum tends to return to its normal position (Courtesy of Dr E P Pendergrass)

Diagnosis —Radiologic examination is of particular value and often establishes the diagnosis It may demonstrate directly not only metallic foreign bodies but also those of less density such as teeth bones or buttons It may present evidence of bronchial obstruction and so indirectly suggest the diagnosis When the foreign body is acting as a ball valve allowing the entrance but not the exit of air the fluoroscope shows some flattening and limitation of excursion of the diaphragm on the invaded side and at the end of expiration some lessened den

cases and autogenous vaccines should be given a trial Bronchoscopic aspirations are often of the greatest value especially in the preparation of the patient for operation

Since however the process once well developed is irreversible the only hope of cure lies in the surgical removal of the affected portion of the lung Before this is undertaken a complete bronchogram is essential in order to determine the location and extent of the lesion In those cases in which only one lobe or indeed one lung is involved and no infection outside the bronchiectatic area is present particularly if the subject is under forty years of age a lobectomy or pneumonectomy is clearly indicated

T Greer Miller

FOREIGN BODIES IN THE BRONCHI

The presence of a foreign body in the bronchial tree may give rise to obstructive phenomena may lead to extensive bronchial disease or may be the important etiologic factor in the development of such serious lung diseases as bronchiectasis or abscess The resultant pathology and symptomatology depend as Tucker has stated upon the size shape and character of the foreign body its length of sojourn the size and age of the host and the relative area of lung involved Instant death may result from suffocation by a large foreign body in the trachea or no symptoms may be produced for months by the aspiration of a small nonobstructive metallic foreign body

Etiology—Children are especially susceptible to the aspiration of foreign bodies though adults are by no means immune Eighty per cent occur in persons under fifteen years of age Carelessness in putting inedible objects into the mouth and hasty eating are the common causes Carelessness in the extraction of teeth or the failure to remove false dentures before anesthesia is sometimes responsible

Morbid Anatomy—The reaction of the bronchial and pulmonary tissue to the presence of a foreign body depends on the character of the body and the degree of bronchial obstruction Metallic substances if nonobstructive may cause no pathology for months Vegetable materials on the other hand such as peanut kernel, bean or watermelon seed whether obstructive or not, frequently give rise promptly to a violent generalized bronchitis and eventually in children, unless the foreign substance is removed to bronchopneumonia If a bronchus is completely closed the corresponding lung collapses or as more often happens becomes filled with secretions and edematous fluid, a condition which Jackson refers to as drowned lung' If the obstruction is only partial and air can pass on inspiration but not on expiration an obstructive emphysema results In other instances the obstruction to both inspiration and expiration is incomplete varying amounts of air enter and secretions accumulate in the lung from time to time Bronchiectasis and lung abscess often result The foreign body enters the right bronchus in 80 per cent of the cases

Symptoms—No symptoms may be noted at the time of the aspiration though usually an attack of choking gagging coughing and wheezing occurs The cause of such an attack is often not suspected especially if a considerable period without symptoms follows the initial reaction If the foreign body however remains in the trachea the cough persists with hoarseness dyspnea and wheezing until the foreign body is coughed up or passes into one of the bronchi Once in a bronchus there may be no symptoms for a period of weeks or months but cough with expectoration eventually develops and the sputum not infrequently becomes blood streaked If the foreign body is of vegetable origin and in a child the symptoms of a violent diffuse bronchitis so called arachidic bronchitis come on promptly with high irregular fever rapid pulse and respiration a distressing cough cyanosis leukocytosis and the other evidences of a grave toxemia A similar severe reaction according to Heatly and Clausen can be produced in rabbits by the injection into the trachea of the fatty acids from peanuts In adults the immediate reaction to such a vegetable foreign body is purely local but later drowned lung' and pulmonary abscess may develop Even the nonobstructive metallic and nonvegetable foreign bodies eventually produce changes that lead to cough expectoration fever

DISEASES OF THE LUNGS

CIRCULATORY DISTURBANCES IN THE LUNG

ENGORGEMENT of blood in the vessels of the lung occurs far more often than has been supposed It is often mistakenly attributed to heart failure but according to newer knowledge congestion of blood in the lung follows or accompanies many other conditions as well The nature of the vast meshwork of loosely supported thin walled capillaries which forms most of the lung parenchyma and contains about 20 per cent of the circulating blood accounts for the ease with which circulatory disturbances occur and can be detected clinically and at necropsy Furthermore the minute ramifications of vasomotor sensory motor and sympathetic nerves extending even to the alveoli suggest the existence of a delicate nervous control which may be easily disturbed by various stimuli

CONGESTION

Two general forms of pulmonary congestion are recognized active and passive

Active Congestion —Active congestion or simple hyperemia of the lungs is a common occurrence especially in its mildest form It accompanies or follows a multitude of general conditions such as strenuous physical exertion, shock infection and fever inhalation of foreign bodies liquids and hot or irritating gas intoxications trauma allergy and vascular and hemorrhagic diseases In the majority of cases the vascular engorgement is mild unimportant and passes unnoticed The chief danger of active congestion lies in the more severe forms when the transudation of fluid fills the alveoli and interferes with the self cleansing process As a result bacteria which gain entrance or happen to be present may find conditions suitable for growth and infection begins It is probable that most cases of pneumonia and other infections of the lung begin in this manner

In the more severe forms of congestion the circulation in the involved area is slowed fluid escapes and floods varying amounts of lung resorption is interfered with and edema of the lungs develops as described on page 831 In the most intense forms of engorgement which may follow shock inhalation of fluids or gases and severe poisoning death may occur in a few hours

Symptoms —The mildest form gives no symptoms or signs When a large enough area of the lung is involved the onset of pulmonary congestion is indicated by the addition of dyspnea and cough to the symptoms of the primary condition When the congestion is intense pulmonary edema occurs with frothy and often blood stained sputum Rales and suppressed breath sounds may be present especially in the dependent portions of the lungs and an increase in the density of the vascular markings may be seen roentgenographically Slight fever may be present even in the absence of apparent infection If infection does occur the signs symptoms and other evidence of atypical pneumonia appear It is often impossible to decide clinically if infection is present or not

Treatment —Treatment of mild pulmonary congestion as such is seldom necessary Correction of the underlying cause must of course be attempted When the engorgement is caused by hypertension and plethora venesection of 250 to 500 cc (8–16 ounces) of blood may cause striking improvement Rest in bed limited fluid and purgation are helpful Treatment of the severe form is described on page 832 (Pulmonary Edema)

Chronic Passive Congestion —The continuous engorgement of the capillaries in the lung is known as chronic passive congestion There are several causes (*a*) mechanical due to some impediment to the drainage of blood as found in certain heart and lung diseases or (*b*) it may be hypostatic in character

Chronic passive congestion may result from any obstruction to the free flow of blood from the lungs to the heart The causes therefore lie in cardiac vascular pulmonary or extrapulmonary disease Among the cardiac diseases of which this is a prominent feature are mitral stenosis or insufficiency congenital defects and myocardial weakness The latter condition may of course be caused by numerous diseases There is a belief that in such cardiac diseases the chronic pulmonary congestion is by no means as mechanical in origin as is usually supposed but represents rather a

sity of the lung on the same side and some displacement of the heart and mediastinal structures toward the uninvolved side On the other hand when the obstruction is complete and atelectasis is present the uninvolved side of the chest shows less density under the fluoroscope and the mediastinal structures are displaced toward the affected side In any event bronchoscopic investigation is indicated for final verification of the diagnosis

The differentiation from diphtheria pneumonia and influenza must be made in the the cases and in many of these only when the patient is moribund The prognosis when the foreign body is not removed is grave On the other hand bronchoscopy as developed by Jackson and his co workers is relatively safe and has led to cure of the pathologic lung changes in 98 per cent of their cases Even in the cases complicated by abscess or bronchiectasis they report a cure in 94 4 per cent When such conditions as cardiac decompensation acidosis dehydration or empyema exist they must be relieved by proper medical or surgical treatment be-



Fig 87



Fig 88

Fig 87—Foreign body in right lung producing emphysema The right lung field shows evidence of hyperventilation The mediastinum is shifted slightly to the left the right dome of the diaphragm is flattened and the intercostal spaces on the right side are widened (Courtesy of Dr E P Pendergrass)

Fig 88—Same case as Figure 87 The expiratory phase shows normal aeration in the left lung field The right lung is still hyperventilated The mediastinal structures show a greater displacement to the normal side (Courtesy of Dr E P Pendergrass)

acute cases and this can usually be accomplished by a careful history and the physical signs though occasionally roentgenologic and even bronchoscopic study may be required Tuberculosis can be distinguished from the more chronic cases by the location of the physical signs the finding of tubercle bacilli in the sputum and radiologic examination It must be remembered however that tuberculosis and a foreign body may coexist

Treatment—The therapeutic indication in all cases is peroral bronchoscopy for removal of the foreign body Such bodies are expelled by coughing in only 2 per cent of fore bronchoscopy is undertaken Under such circumstances Tucker regards the risk of the procedure as trivial

T Grier Miller

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DISEASES OF THE LUNGS

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protective mechanism designed to relieve the heart by pooling a considerable volume of blood in the capillary bed of the lungs thus reducing the amount of blood which the heart must keep in circulation at nearly constant speed It may be therefore the physiologic equivalent of hemorrhage or venesection

Chronic passive pulmonary congestion may develop also as the result of obstruction to the pulmonary circulation due to diseases of the lungs as in cases of hypertrophic pulmonary emphysema fibrosis, sclerosis, atelectasis pneumonoconiosis chronic abscesses, bronchiectasis or tumors and in mediastinal tumors which press against or invade the pulmonic veins

Pathology —Lungs the seat of long standing chronic passive congestion, are heavy and have a typical russet brown color (brown induration of the lung) The cut surface, sometimes dry, sometimes edematous has a brownish red hue The capillaries of the alveoli are overdistended with blood their walls show evidence of degeneration and desquamation and the air spaces contain a slight amount of serum red cells and macrophage cells filled with granules of hemosiderin In long standing cases there is marked increase in the interalveolar connective tissue (see Fibrosis p 847)

Symptoms —Chronic passive congestion even when marked in patients with heart disease may give no pulmonary symptoms as long as cardiac compensation is well maintained This is surprising in view of the increased rigidity of the lungs and the marked overfilling of their capillaries During this stage however the patient is susceptible to attacks of bronchitis With developing cardiac decompensation and the resulting slowing up of the pulmonary circulation certain pulmonary symptoms become manifest Among these are dyspnea cough and the expectoration of sputum which may for a long time be uniformly rusty or marked by rusty streaks and dots This color is due to masses of the characteristic heart failure cells which are phagocytic mononuclear cells filled with granules of modified free hemoglobin In such cases the sputum frequently is also definitely blood tinged and small pulmonary hemorrhages occur frequently

This occurrence often leads to a diagnosis of unsuspected stenosis of the mitral valve The portions of the lung involved in the process are common sites for the development of atelectasis or pneumonia

Dulness rales and suppressed breath and voice sounds are usually present over the involved areas Cyanosis and dyspnea are common Abnormal density and increase in the shadows of the vascular markings are found in the roentgenogram Fever may be absent but is often of low grade especially if infection occurs which it commonly does

Hypostatic Passive Pulmonary Congestion —Quite different from the mechanical form of congestion is a condition characterized by stagnation of blood in the dependent portions of the lungs It may develop during *protracted fevers* as typhoid and in those adynamic states which result from unconsciousness long debilitating diseases malnutrition cachexia and senility, particularly when the patient lies for a long time in one position

Hypostatic congestion may develop in the lower lobes long collapsed because of a high position of the diaphragm, as in cases of ascites meteorism or abdominal neoplasms also in cases of brain injury or organic disease of the brain *At necropsy*, the posterior inferior or dependent portions of the lower lobes of the lungs are dark in color and so soggy with blood and serum that the alveoli may no longer contain air Gravitation doubtless determines the localization of hypostatic congestion but this alone is not sufficient since it does not occur in healthy persons and in certain sick ones no matter how long they remain in one position in bed Long continued hypostatic congestion may so lower the resistance of the lung tissue to secondary infections that a low grade chronic pneumonia may develop

Symptoms —The symptoms of hypostatic congestion are not characteristic They include cyanosis respiratory distress and cough with abundant sputum containing heart failure cells On physical examination tactile fremitus is decreased and percussion may reveal slight dulness on auscultation feeble sometimes blowing breath sounds with showers of crackling rales are heard Pneumonia is suggested by a low fever physical signs suggestive of pulmonary con

solidation and shadows in the roentgenogram

Treatment—To forestall the development of hypostatic passive congestion all patients with long standing asthenic or debilitating conditions should be taught to practice deep breathing exercises regularly Deep breathing may be induced by administering with a face mask gas composed of carbon dioxide 5 parts and oxygen 95 parts The application of the mask should be intermittent the time determined by the patient s response and comfort Their position in bed should be changed from time to time and if possible they should be allowed to sit up in a chair The treatment of this condition is that of the condition inducing it and should include all measures that may bring about an improvement in the patient's general condition Attention should be given to improving the patient s morale with psychotherapy physiotherapy and proper diet

HOBART A REIMANN

PULMONARY EDEMA

In pulmonary edema there is a sudden or gradual escape of serous fluid from the capillaries into the lung tissue the alveoli bronchioles and often into the bronchi A part or the whole of one or both lungs may be involved In some cases edema seems to be an extreme stage of acute or chronic congestion and in others to arise from a number of other conditions In most instances edema of the lungs seems to be one factor in a general systemic collapse but it may occur as an isolated incident without other evidence of circulatory failure All grades of severity are encountered from the mildest which is common to the severe fulminating form with early death from suffocation

Etiology—*The Mechanical Group*—Weakness of the left ventricle and back pressure into the blood vessels of the lung was long thought to be the chief cause of pulmonary edema but in a critique of the subject Luisada concludes that this theory is inadequate nor is there direct evidence favoring a purely neurogenic theory The cause is not definitely known and seems to be a combination of factors in most cases When a tendency toward the occurrence of edema of the lungs is present, stasis or an increase in pulmonary blood volume favors its development Increased permeability of the capillary walls brought about by vasomotor reflexes may take place This may explain the edema which occurs in shock angioneurotic edema or epilepsy Pulmonary edema may develop in valvular heart disease pericarditis aortitis angina pectoris coronary thrombosis pulmonary infarction drowning and during nephritis especially in advanced nephrosclerosis arterial hypertension and uremia

The Infectious Group—Acute pulmonary edema may complicate many of the acute infectious diseases In these it may be a terminal event The cause is not clearly understood but is believed by some to be the result of a toxic effect on the centers controlling the vasomotor system of the lungs or following collapse and failure of the circulatory system with pulmonary edema as a result

The Toxic Group—Patients severely poisoned by various substances such as alcohol barbital compounds iodine morphine epinephrine and asphyxiating gases may develop pulmonary edema In these it may be caused by the same neurogenic factors discussed in the infectious group Edema may of course follow the inhalation of numerous irritating gases as commonly used in commercial fields and in warfare The edema and suffocation may occur immediately after exposure or may be delayed for many hours and develop suddenly after a period of relative well being

Other Causes—In women more cases of pulmonary edema develop during pregnancy and confinement than in those with primary cardiac conditions Some have recommended therapeutic abortion in women who become pregnant after surviving a previous attack Pulmonary edema is also noted at times in diseases of the central nervous system such as trauma to the brain myelitis cerebral embolism and thrombosis In rare cases and for unknown reasons it has followed thoracic and abdominal paracentesis Pulmonary edema is common in shock

Pathology—The generally edematous lung is found at necropsy to be *anemic* heavy and sodden It pits on pressure and when incised large quantities of clear or

blood tinged foamy serum flow from it It may in places have a gelatinous aspect

Symptoms—The onset of edema may be gradual or sudden and is manifested by a feeling of oppression or pain in the chest, and rapid breathing with dyspnea or orthopnea There may be an incessant short cough, and a copious frothy sometimes blood tinged fluid gushes from the mouth and nose The face becomes pale and covered with cold sweat, the pulse is feeble and the heart s action weak Over the entire chest piping and bubbling rales may be heard The temperature and blood pressure fall An attack may be fatal in a few hours in other instances symptoms persist for twelve to twenty four hours and then disappear Repeated attacks may occur When fatal the edema usually develops slowly and insidiously with coma and is manifested at first by coarse moist rales throughout the chest which soon obscure all other lung and heart sounds and later become audible even at a distance (the so called death rattle') In the advanced stage streams of foamy fluid slowly pour from the nose and mouth The prognosis is always grave

Treatment—The management varies with the cause A primary condition if not evident should be sought for and appropriately treated When pulmonary edema is threatened the fluid intake should be promptly but temporarily reduced Aromatic spirits of ammonia 4 cc (1 drachm) may be given by mouth In general patients should be treated as for shock Bed rest and maintenance of body warmth is important In plethoric or hypertensive patients venesection of 250 to 500 cc (½–1 pint) of blood often results in striking improvement Amyl nitrite 0 3 cc (3 minims) by inhalation or sodium nitrite 0 06 Gm (1 grain) by mouth are said to be of value This procedure of course is not indicated in shocklike conditions with collapse and hypotension In the latter case sucrose in 100 cc doses of a 50 per cent solution may be injected intravenously This form of treatment unfortunately is seldom helpful because the problem is not especially one of loss of fluids but of failure to keep the fluid in the circulatory system moving Epinephrine hydrochloride 1 cc (15 minims) may be added to the solution or injected subcutaneously in an attempt to restore the blood pressure Atropine is traditionally recommended by some to dry up the secretions' but it is doubtful if it exerts any more effect on edema of the lungs than on edema elsewhere It may actually be harmful by speeding the heart rate Nevertheless many give it hypodermically in large doses 1 2 mg (1/50 grain) and claim success

Morphine sulfate in doses of 15 mg (¼ grain) tends to relieve edema of the lungs by lowering the excitability of the central nervous system It should not be given in states of collapse

Transfusion of blood (250 cc to 500 cc.) may be indicated for anemia and transfusion of plasma (16 to 32 Gm) for hemoconcentration or loss of blood volume unless heart failure is present

Oxygen Therapy—The inhalational treatment of pulmonary edema is in the first place the provision of a high oxygen concentration between 50 and 100 per cent oxygen The specific procedure which has been found valuable is the application of positive pressure between 2 and 5 cm. of water Although the helmet hood apparatus, which provides positive pressure in inspiration and expiration is the most effective method of applying this therapy, a similar method has been successfully employed namely an adaptation of the meter injector mask which consists of a metal disc enclosing the expiratory valve and perforated with variable sized orifices When expiration is conducted through a restricted orifice a positive pressure is developed which is directed backward against the pulmonary epithelium and tends to prevent transudation of serum The positive pressure first employed is 3 or 4 cm of water and is gradually lowered at the rate of 1 cm of water every one to four hours depending upon the clearing of edema and the condition of the individual patient The administration of positive pressure in conjunction with 100 per cent oxygen may be also used in cases of pulmonary edema due to industrial and war gas poisoning In medical or surgical shock, in which there is a deficient return of blood to the heart the increased intrapulmonary pressure may further retard the entrance of blood into the right auricle Positive pressure under these circumstances should be

applied only on expiration and cautiously for short periods at a time only If it is followed by a drop in the systolic blood pressure of more than 10 mm Hg the positive pressure should be lowered or dispensed with However in pulmonary edema as a complication of pneumonia heart disease or increased permeability of the capillaries it is frequently of great value and may be used until the edema clears If there is a return of pulmonary edema positive pressure should again be applied and the attempt made to lower the pressure gradually

Patients who have repeated attacks of pulmonary edema should be warned against overexertion or other activities likely to bring on an attack If pulmonary edema accompanies labor the uterus should be emptied

HOBART A REIMANN

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PULMONARY HEMORRHAGE

Bleeding from the lungs occurs in two forms in one the blood pours into a bronchus or open pulmonary cavity from a ruptured blood vessel and is immediately expectorated as a bright red fluid either pure or mixed with sputum or if temporarily retained as a dark brown or black material often in clots In the other form it passes into the alveoli or interstitial tissues by diapedesis or rupture of capillary walls and is expectorated as blood stained sputum either bright red or more usually brownish from modified hemoglobin The first form is by far the more dangerous The difference between the terms hemoptysis and hemorrhage is in the quantity of blood raised Amounts less than 4 cc (1 drachm) are usually regarded as hemoptysis

Bleeding from the lungs occurs most commonly in pulmonary tuberculosis and bronchiectasis It may be the first sign of either disease In both diseases it results from the erosion of veins or arteries in the ulcerative process The amounts raised in the sputum may be insignificant or large enough to cause early death from hemorrhage especially if an artery is opened Hemorrhage may be a single event or it may be intermittent or continuous for several days In most cases only a portion of the blood is expectorated the remainder is either swallowed or enters the dependent portions of the lung where atelectasis and a low grade inflammatory process may begin which slowly disappears as the blood is absorbed

In a considerable number of cases the cause of pulmonary hemorrhage is never determined In rare cases in women it occurs during the menstrual period and has been considered as vicarious menstruation' Hemorrhage from the lung in the menstrual period is common in tuberculous women and in those with hemorrhagic diseases Hemorrhage may occur in severe hypertension

Bleeding from the lungs may occur in many other pulmonary diseases such as chronic fungous or parasitic infections neoplasms cysts gangrene abscess emphysema atelectasis arteriosclerosis trauma and amyloid disease True hemoptysis is not a feature of pneumococcic pneumonia in which the color of the sputum is due to the gradual seepage of blood into the alveoli Hemoptysis is however a frequent occurrence in Friedlander s bacillus pneumonia in its acute or chronic form The sputum in whooping cough is often bloody Gun shot and stab wounds must be mentioned

Numerous other nonpulmonary diseases are occasionally characterized by hemoptysis Small amounts of blood are frequently raised in mitral stenosis Ulcerations in the larynx trachea and bronchi and rupture of an aneurysm into the respiratory tract may lead to fatal hemorrhage Pressure of an aneurysm or new growth from without or the presence of a foreign body may cause hemoptysis over long periods Widespread and intense capillary congestion with rupture and hemorrhage into the walls of the small bronchioles and alveoli of both lungs occurs in pulmonary concussion as a result of proximity to the detonation of high explosives (page 835)

Scurvy and diseases of the blood such as purpura granulocytopenia hemophilia and leukemia may cause hemoptysis

Symptoms —Severe hemoptysis occurs as a gush of blood bright or dark red in

color which may flow from the mouth almost without coughing Warning may be given by the previous appearance of slight blood stains in the sputum Hemoptysis as a rule appears suddenly, often without warning other than the desire to cough, or the sudden presence in the mouth of a warm salty fluid Slight hemorrhages may be single or may recur for days followed for several more days by blood tinged sputum In contrast to these are the profuse hemorrhages sufficient even to drown the patient, which follow the erosion of a large pulmonary blood vessel or the rupture of an aneurysm

Diagnosis —When hemoptysis occurs the chest should at once be thoroughly examined by auscultation in order to determine if possible from which lung the bleeding comes A history should be immediately obtained from the patient, or from some relative or friend so as to determine the cause of the hemorrhage If feasible a roentgenogram should be made at the bedside with a portable apparatus The movement of the patient to allow this examination is not as dangerous as is usually assumed In cases of repeated hemoptysis of doubtful etiology laryngoscopy or bronchoscopy should be performed by an expert since not only may the bronchus leading to the bleeding area be thus identified but it may be discovered that instead of being a pulmonary lesion the hemorrhage originates from an ulcer in the trachea or large bronchus and the lesion may be so situated that it can be treated locally Appropriate tests should be employed for all diseases listed as possible causes

Blood from the lungs is alkaline and frothy in contrast with that coming from the stomach which is apt to be acid often granular and darker in color Blood from the lung may of course be swallowed and later vomited

Prognosis —Small pulmonary hemorrhages may by relieving pulmonary congestion actually prove beneficial Unless very profuse hemoptysis seldom is immediately dangerous In the great majority of cases it soon ceases spontaneously The immediate dangers of profuse hemorrhage are death by suffocation, spread by the blood of the germs of the underlying infection aspiration pneumonia massive collapse of a lobe or of a lung either from spasm of its bronchus or from its occlusion by a blood clot, and the weakness or shock due to the resulting anemia

Treatment —Any underlying cause if present should be found and eliminated In the majority of cases of hemoptysis either the patient is dead before the treatment can be begun or the bleeding has already stopped spontaneously If in the case of profuse hemorrhage the patient can be kept alive for twenty four hours, the immediate prognosis is good Often the syncope induced by the sudden loss of considerable blood saves life by promoting thrombosis All diet and previous medication should at once be stopped The patient should lie on the affected side in order to protect the sound lung from the free blood in the trachea and bronchi An ice bag placed against the side of the chest has much the same value as a sand bag which by its weight immobilizes the chest The main therapeutic procedures to be recommended are absolute rest in bed, reduction of the blood pressure if it is abnormally high by a minimum diet purging and measures to allay the cough Peace of mind is of great importance but is most difficult to attain because of the frightened state of the patient It should be secured by calmness and reassurance but often a hypodermic injection of morphine 0 01 Gm (1/6 grain) or more is necessary For the cough which is usually present and disturbing opium should be given to lessen but not to suppress it The patient should be instructed not to cough unnecessarily or too hard A moderate amount of cough is desirable to clear the lungs and bronchi of blood The patient may be allowed to suck small pieces of ice In some protracted cases of bleeding artificial pneumothorax has stopped the hemorrhage

Theoretically it would seem desirable to reduce the frequency of the heart beats to lower the general blood pressure and to increase the coagulability of the blood The drugs commonly used however seldom accomplish these purposes indeed some of them raise the peripheral blood pressure and therefore may be harmful This appears to be true of digitalis and of ergot while the nitrites tannic acid and lead are of little or no value On the other hand aconite atro

pine and pituitary extract seem to reduce the pressure in the lesser circulation and, therefore may be helpful One of the most satisfactory means of lowering the general blood pressure in plethoric hypertensive patients is purgation and when the bleeding is protracted saline cathartics should be given in repeated doses Alcohol should never be allowed A transfusion of 100 cc of blood may control the bleeding It is said that intravenous injections two or three times daily of 10 units of parathyroid hormone sometimes succeed after other methods have failed Other measures advocated are the prompt intratracheal injections of adrenalin or better some say of distilled water which produces reflex contraction of the bronchi

For the treatment of severe and repeated hemorrhages the following surgical measures have been advocated phrenic exeresis pneumothorax the division of pleural adhesions extrapleural pressure against the lung thoracoplasty

HOBART A REIMANN

PULMONARY CONCUSSION

(*Lung Blast*)

Diffuse capillary hemorrhage of the lungs resulting from close proximity to the detonation of high explosives occurs in civil life but has become much more frequent with military bombing The majority of cases occur in persons bombed in closed spaces The lesions consist chiefly of bleeding from the alveolar capillaries In severe cases massive hemorrhages and rupture of goblet cells occur with the liberation of much mucus Both lungs are usually affected

Symptoms —All grades of severity occur depending upon the force of the explosion the distance from it the environment and the condition of the patient Death may be instantaneous without outward signs of injury but the majority of cases are less severe and most patients recover There is usually prostration dyspnea tachycardia and oppression or pain in the chest Cough and fever develop later Physical signs vary from those of congestion to consolidation Bulging of the chest is noted Mottled areas of density are seen in roentgenograms As in other forms of shock the onset of symptoms may be delayed for many hours All persons close to an explosion particularly in enclosed spaces should be confined to bed and observed for at least twenty four hours The treatment is the same as that for the general management of shock or of pulmonary hemorrhage (p 834)

Treatment.—Heat oxygen morphine and transfusion of plasma are of greatest value Intravenous injection of fluid should be given with caution to avoid pulmonary edema Incorrect methods of artificial respiration may cause further harm Complications or sequels such as shock or pneumonia should be anticipated Other visceral injuries sustained at the same time must be suspected If an anesthetic for surgical purposes is required it should be given intravenously

HOBART A REIMANN

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PULMONARY INFARCTION—PULMONARY EMBOLISM AND THROMBOSIS

A pulmonary infarct consists of a mass of airless lung tissue infiltrated with blood which has extravasated into the air cells and interstitial pulmonary tissue The condition results from closure by an embolus or thrombus of the pulmonary artery supplying the affected area The lung tissue in the infarct does not as a rule become destroyed unless the collateral circulation is also impaired

An embolus or thrombus large enough to close a main pulmonary artery or one of its largest branches causes widespread pulmonary edema without hemorrhagic consolidation and promptly proves fatal Atelectasis may occur as a result of bronchial constriction caused by a reflex reaction The occlusion of one of the medium sized branches often produces a hemorrhagic infarct but not always Indeed the closure of even moderately large branches of the pulmonary arteries may do no harm unless the lung already is the seat of chronic passive congestion as in some types of heart disease

Incidence—Many emboli which reach

the lung are fragments of mural thrombi so *common in the right auricle* in cases of bacterial endocarditis and auricular fibrillation in which slowing of the blood stream seems to be an important factor Others arise peripherally especially from phlebitis in the legs and from the pelvis in cases of pregnancy puerperal sepsis pelvic inflammatory disease and prostatitis *Pulmonary* vessels may be closed also by thrombus formation with an infarct often the result This occurs in some of the acute infections such as typhoid and in all conditions in *which the blood flow in the lesser circulation* becomes greatly retarded Changes in *the composition of the blood* such as occur in hyperinosis and thrombocytosis and perhaps a decrease of antithrombin and heparin may also play an important role by increasing the tendency to clot

Pulmonary infarction is the immediate *cause of about 2 per cent of all deaths* it is found in nearly 4 per cent of all necropsies on children In surgical practice emboli to the lung explain 50 per cent of all important postoperative complications while 50 per cent of all deaths following pelvic operations are due to pulmonary complications some of them embolic in origin and others atelectatic Any patient with bacterial endocarditis phlebitis auricular fibrillation or with a history of recent surgical operation or severe trauma is in danger of pulmonary embolism The condition is three times as common in obese as in slender persons and is most common between the ages of forty and sixty

Symptoms—The *symptoms of lung infarction*, when typical are a sudden piercing pleural pain which radiates to the shoulder dyspnea sudden in its onset, often with signs of collapse an irritating cough with hemorrhagic sputum or small hemoptyses and occasionally an annoying continuous hiccough The patient looks anxious is cyanotic has *tachycardia* and sweats profusely On physical examination if the *infarct is* large and favorably located there is a local area of impaired resonance a localized friction rub distant bronchial breath sounds and moist rales The patient expectorates round nummular masses composed of more or less thoroughly mixed mucus and blood which remain discrete in the cup Fever or leukocytosis is usually present but may be absent Jaundice is occasionally present In about 15 to 20 per cent of the cases with such signs the patient dies In cases of rapidly fatal pulmonary embolism or *thrombosis the patient feels a sudden pain* or sense of tightness in the chest especially under the sternum He becomes ashen in color anxious and then cyanotic and dyspneic Pulmonary edema develops, the pulse becomes feeble or imperceptible, death follows in from a few minutes to several hours Some infarcts cause characteristic symptoms *but no physical signs* and others the opposite or neither Embolic lung infarction following surgical operations usually develops within the second or third week that following trauma such as a fractured bone during the fourth or fifth week after the injury During the above mentioned periods the temperature usually rises to 99° or 100° F daily—evidence possibly of thrombophlebitis In such cases however the emboli are small and seldom of themselves prove fatal Symptoms of pulmonary *fat embolism* particularly from fractured bones arise several hours or days after the injury

In some instances the circulation becomes reestablished and the extravasated blood is *eventually removed or the infarct ultimately* becomes a pigmented, puckered fibrous scar Secondary infection of the infarct may lead to sloughing abscess or massive necrosis with cavity formation If such an infarct ruptures into the pleural cavity it produces pneumothorax or pyopneumothorax

Pathology—Infarcts vary in size from *that of a pea to that of an orange* and average 3 × 2 × 1 cm in size They are irregular in shape and are almost always in contact with the pleura *Often they are* multiple The majority of them are in the lower lobes

Recent infarcts are dark but those a *little* older are reddish brown in color They are hard and firm and on section look like ordinary blood clots Microscopic examination shows that the air cells and alveolar walls *are distended with red blood corpuscles*

Diagnosis—Small infarcts seldom are correctly diagnosed usually such conditions are interpreted as pleurisy, *pneumonia* atelectasis or coronary occlusion In some cases however the symptoms and physi

cal signs of infarction are quite unmistakable Some infarcts even large ones fail to render the sputum bloody Sometimes hemoptysis is the only sign of infarction and its appearance in cases of heart disease particularly mitral stenosis should always suggest the possibility of this lesion although in the majority of cardiac patients such hemorrhages usually are due to pulmonary congestion Often an infarct gives no physical signs but of those which are obtained a pleural friction rub is the most constant Unexplained fever or jaundice dyspnea cyanosis tachypnea tachycardia hemoptysis and prostration are all important diagnostic clues



Fig 89—Infarcts in the right lower lobe The patient had hypertension and at necropsy three weeks after the roentgenogram was made mural thrombosis of the right auricle and the remains of pulmonary infarcts were found (Courtesy of Dr L. G Rigler)

Roentgenograms though seldom convincing are often suggestive (Fig 89) Infarcts appear as areas of localized haziness or as small irregularly shaped shadows Evidence of atelectasis may be present

Prevention —Attempts should be made to combat or neutralize those factors known to favor the development of infarcts namely slowing the blood stream and an increase of the elements concerned in the clotting of blood Patients should not be completely immobilized as a certain amount of movement favors the maintenance of the speed of circulation Deep breathing exercises are of value Little can be done to alter the composition of the blood except to give heparin and thus render the blood less coagulable To prevent postoperative thrombosis or thrombophlebitis heparin has been given intravenously either intermittently or continuously with reported success (Mason)

Treatment —When infarction occurs the patient should remain quietly in bed Morphine sulfate 15 mg (¼ grain) repeated in fifteen to thirty minutes is the most valuable drug to relieve pain dyspnea and apprehension It should be used even in the presence of cyanosis or collapse If shock develops treatment is the same as described for Pulmonary Edema (p 832) The intravenous injection of papaverine hydrochloride 0 03 Gm (½ grain) and atropine sulfate 0 45 mg (1/150 grain) has been recommended by some to block off vagal effects and relieve spasm of the bronchi and blood vessels The injection may be repeated Oxygen therapy may relieve dyspnea and cyanosis Heparin has been used with success to render the blood less coagulable

HOBART A REIMANN

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PULMONARY ATELECTASIS

(*Simple Atelectasis Massive Pulmonary Atelectasis or Collapse*)

Atelectasis or collapse of the alveoli of the lungs occurs far more commonly than is generally believed Physiologic atelectasis occurs during rest

Simple Atelectasis —A multitude of diseases or conditions of the lung including infections surgical operations shock edema trauma pulmonary embolus and infarct foreign bodies in the lungs or bronchi, irritants extra pulmonary pressure and nervous factors may cause a functional failure of greater or lesser numbers of alveoli This results in partial or complete deflation and immobilization in the deflated state Atelectasis is especially common in influenza and often occurs during tuberculosis and other forms of pneumonia Its presence often confuses the physical findings of the primary disease The existence of collateral respiration recently discovered is no doubt a great factor in preventing serious collapse from occurring more often than it does

There are no signs or symptoms if small areas of lung are involved But if enough pulmonary tissue is affected there may be dyspnea tachypnea cyanosis and tachycardia The physical signs vary greatly They are chiefly those of suppression of breath and voice sounds and rales Dulness is not evident unless large portions of lung near the pleura are collapsed The signs are often transient and migrate from place to place as old areas clear up and new ones form The signs may change considerably when the patient rolls from one side to the other

Treatment is seldom necessary but frequent change of the patient s position and deep breathing exercises may be helpful in preventing the condition or in clearing it up Sedatives and oxygen may be helpful for severe dyspnea Abdominal distention and tight binders should be avoided Circulatory failure if present should be appropriately treated

Massive pulmonary atelectasis implies the sudden and complete collapse of one or more lobes of one or both lungs (Fig 90) The etiology of the condition is unsettled the chief causes are believed to be (*a*) sudden obstruction of the bronchi (*b*) pulmonary infarct (*c*) infection, (*d*) allergy and (*e*) nervous stimuli The majority of cases follow anesthesia and *surgical operations* especially on the abdomen or after some physical injury The occasional presence of plugs of mucus in the bronchi supplying atelectatic lobes suggests their causative role in this condition but mucous plugs may be the result and not the cause of the disturbance Massive collapse also follows acute bronchial obstruction or trauma from any cause asthma pneumonia tumors swollen lymph nodes (Fig 90) pleurisy foreign material (blood water solids) in the lung external pressure nervous shock spontaneous or induced pneumothorax and many other conditions It may be the cause of death in these disorders

The area collapsed usually reexpands rather promptly when the cause is removed Prolonged collapse may result in permanent fibrosis

Pathology —At necropsy in cases of massive collapse the mediastinum and heart are pulled toward the affected side of the thorax, the diaphragm on that side is high and the lung is collapsed firm and so airless that it sinks in water One lobe or an entire lung may be involved the right three times as often as the left There is *compensatory* emphysema of the other lung The condition sometimes is bilateral Evidence of closure of the bronchus is not always found

Symptoms —The fully developed symptom complex of massive pulmonary collapse is unique since it appears in no other condition The symptoms in postoperative cases commence within twenty four to forty-eight hours They may be mild or so severe as to cause sudden death The onset usually is sudden with dyspnea tachypnea cyanosis tachycardia prostration and pain usually in the lower part of the thorax The patient

sits up in bed, is cyanotic and breathes rapidly His facies expresses great anxiety and yet he does not really look sick if he does it is from some associated condition The same is true even if cough and sputum are present The temperature ranges from 100° to 104° F The pulse rate varies from 110 to 130 the respiratory rate from 40 to 50 per minute and the leukocyte count from 10 000 to 20 000 per cubic millimeter

Physical Signs —Of the physical signs of massive collapse the most characteristic or less flat especially posteriorly If the condition affects the right side the flat note over the lower chest is explained in large part by the high position of the liver The voice sounds are absent or diminished according to the degree of collapse and the breath sounds are suppressed but bronchial if the collapse is not complete in which case the breath sounds are inaudible Local rales coarse and often musical in character are heard but only while the collapse is developing or subsiding Distant rales also may be

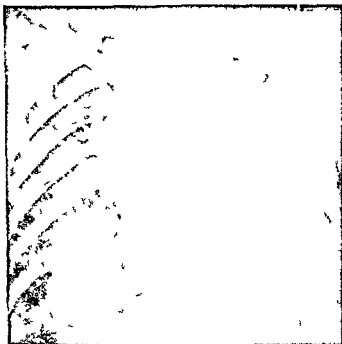


Fig 90—Massive atelectasis of the left lung The patient, aged 22 had Hodgkin s disease of the mediastinal lymph nodes A previously made roentgenogram showed extensive widening of the mediastinum with displacement of the esophagus to the right There were physical signs of emphysema in the left lung and the patient was dyspneic and cyanotic

The roentgenogram above made a week later shows the heart and mediastinum pulled to the left, the left half of the diaphragm elevated and the intercostal spaces narrowed on the left and broadened on the right. The collapse occurred without clinical symptoms but the physical signs consisted of dulness with absent breath and voice sounds over the left lung

are those which indicate that the heart mediastinum and diaphragm are moved toward the affected side and that the other lung is overdistended The chest wall on the affected side looks flat its intercostal spaces may be narrowed or depressed its respiratory movements are diminished or absent and sometimes are reversed those of the normal side are excessive On the affected side the vocal fremitus may be decreased or absent according to the degree of atelectasis the note on percussion is more heard The percussion note over the unaffected side on the other hand is hyperresonant since this lung is emphysematous its margins extend beyond their normal limits The elevation of the diaphragm and dislocation of the mediastinum may persist after all pulmonary symptoms have disappeared

Diagnosis —In the diagnosis of massive collapse of the lung the most important single point is the displacement of the heart toward and the high position of the diaphragm on the affected side This should

be verified by a roentgenogram Other points of great weight are the sudden onset of the illness with cyanosis and increased respiratory rate and the marked discrepancy between the extensive physical signs and the absence of malaise While the diaphragm is high and immobile it is not quite as immobile in spontaneous collapse as in collapse due to foreign body in a bronchus At first one may suspect lobar pneumonia pleurisy with or without fluid pneumothorax pulmonary embolus or thrombosis or diaphragmatic hernia Roentgenograms will show on the affected side a dense shadow which represents the collapsed lung, heart mediastinum, and diaphragm (Fig 90)

Prognosis —The prognosis is usually good the condition disappearing in a week or ten days *unless the primary disorder is permanent* or serious it is bad if the collapse is bilateral or persistent or if pneumonia follows

Treatment —The cause if present should be removed If the collapse is due to bronchial obstruction bronchoscopy may be necessary Small doses of morphine sulfate 0 01 Gm (1/6 grain) may be helpful if the patient is excited or distressed by the dyspnea The patient should be rolled from side to side or should lie with the affected side up to facilitate the drainage of secretion Deep breathing should be encouraged and if it fails a mixture of oxygen 95 per cent and carbon dioxide 5 per cent should be *given by inhalation If atelectasis* is caused by bronchoconstriction resulting from reflex stimulus De Takats recommends the intravenous injection of atropine sulfate 0 45 mg (1/150 grain) and papaverine hydrochloride 0 03 Gm (1/2 grain) to block off vagal effects and to cause vasodilation

Prevention of atelectasis after surgical operations is more important than treatment After operation the patient should not be deeply narcotized and tight binders should not be placed about the chest or upper part of the abdomen The patient s *position* in bed should be occasionally changed and deep breathing encouraged Collections of secretion in the oropharynx *should* be aspirated It is important to keep the patient warm comfortable and reassured

HOBART A REIMANN

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ABSCESS OF THE LUNG

Definition —Abscess of the lung is a localized area of suppuration in the lung with *or without cavitation It is* accompanied by more or less necrosis of tissue which if massive is usually called gangrene

Abscesses may be classified as (*a*) single unilocular or multilocular central or peripheral closed or open to the bronchus or pleura and (*b*) multiple in one or both lungs In one series of 315 cases (Maxwell) examined postmortem instances of single abscess numbered 199 and of multiple abscesses 116 They may also be classified as primary and secondary Many chronic abscesses are surrounded by areas of bronchiectasis

Etiology —The bacterial cause of lung abscess in most cases is confused since a variety of micro organisms is usually present In certain instances however especially early in the disease bacteria such as Friedlander s bacilli staphylococci certain fungi *Endamoeba histolytica* and others may be found alone Streptococci colon bacilli Welch bacilli anaerobes and other bacteria including fusiform bacilli *and spirochetes* which are very frequently found seem to be secondary invaders which probably intensify *and prolong the* disease and cause the unpleasant odor so often noted The lesions caused by *Bacillus tuberculosis* are regarded separately from lung abscess

Except for the few specific infections listed above which may be regarded as ' primary infections though in perhaps all cases some preceding condition is *present most* cases of lung abscess are brought about by the invasion of a mixture of ever present mi

croorganisms which grow in tissue altered or damaged by a variety of causes Such damage may arise from inflammation materials aspirated into the lung emboli or other causes

The most common causes of abscess are (a) operations on the oropharynx (tonsillectomy) especially under general anesthesia (b) acute pulmonary inflammations (c) abdominal operations, (d) neoplasms of the bronchi lungs or esophagus (e) bronchiectasis (f) trauma contusion from penetrating wounds or fractured ribs (g) foreign body in the bronchus (h) bacteremia

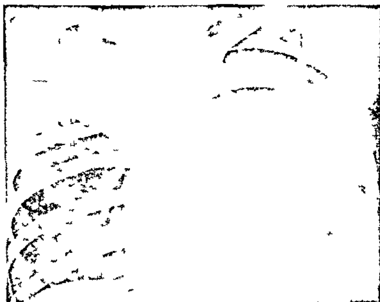


Fig 91—Acute abscess of the lung with cavity formation fluid level and peripneumonitis in the right upper lobe The large area in the left lung interpreted as being pneumonia, later broke down to form another abscess It represents the early stage of lung abscess The patient had granulocytopenia and died (Courtesy of Dr K. Kornblum)

from infection elsewhere in the body (i) infarcts and (j) submersion in and/or aspiration of liquids

Lung abscess rarely occurs as a complication of lobar pneumonia unless secondary invasion with staphylococci occurs but minute multiple abscesses are often found post mortem especially in patients with Type III pneumococcus pneumonia in whom the disease has been prolonged Abscess apparently occurs more often in certain forms of atypical pneumonia (Fig 91) particularly that caused by Staphylococcus aureus (Fig 92) in which miliary abscesses are present early Abscess following abdominal operations may be due either to emboli or it may follow postoperative pneumonia, atelectasis or the aspiration of vomitus or other foreign bodies Rupture of pus through the diaphragm may be a cause Recent statistics indicate that the apparent increase in pulmonary neoplasms causes an increasing number of secondary lung abscesses The development of a secondary abscess may be the first indication of neoplasm as well as of foreign bodies

Pathology—The right lung is more often involved than the left and the lower lobes more than the upper ones Both lungs are usually involved in cases of multiple abscesses Associated conditions such as empyema pleurisy pyopneumothorax and pericarditis often occur Amyloid disease pyemia abscess of the brain and mediastinitis may follow in prolonged cases

Unless the abscess is primary the lesions associated with the previous disease are present In many cases the earliest changes may be those of pneumonia or pneumonitis (Fig 91) but in others the process begins with necrosis Abscesses may be single or multiple and in certain cases multiple abscesses coalesce to form a large single one (Fig 92)

The size of pulmonary abscesses varies from that of a pinhead to that of an orange The larger cavities if *recent or advancing* have ragged walls of necrotic lung tissue surrounded by a zone of hyperemia and con tain purulent blood stained and often fetid fluid debris the older lesions gradually be come enclosed by a thick fibrous wall Em bolic abscesses often numerous are located as a rule just beneath the pleura These often start as irregular infarcted areas which at first are firm grayish red in color and surrounded by a zone of intense hyper emia, but as their centers soften they may *perforate into a bronchus or through the* pleura in the latter case giving rise to pyo pneumothorax

Drainage *through the bronchus may* be obstructed by formation of granulation tis sue by the bronchial mucosa The abscess may heal after its evacuation and *leave no* trace it may disappear by spontaneous re sorption without drainage or it may be come walled off with *fibrotic tissue and* result in a chronic abscess or in a cyst Fibrosis in and around the area with dense pleural adhesions, calcification and de formity of the chest wall is common

Symptoms—As a rule the early symp toms of 'primary' lung abscess are regarded as those of bronchitis grippe or pneumonia By the end of the second week however the patient may suddenly expectorate pus which may or may not have a foul odor Cough is present sooner or later in almost all cases and may be the first symptom If the abscess ruptures cough is distressing Pain referred to some part of the chest is often noted early It may resemble pleuritic pain and is made worse by deep breathing *Small hemoptyses may occur* Fever is pres ent from the onset and may be high later the temperature curve becomes remittent *and characteristic* of sepsis with chills sweats loss of weight and strength and anemia Clubbing of the fingers may be *noted after a few weeks* No doubt many lung abscesses occur without ever being rec ognized They may run their course with *spontaneous cure* by evacuation or absorp tion

Lung abscess developing after aspiration



Fig 92—Multiple abscesses in both lungs following staphylococcic pneumonia The roentgenogram was made twenty-eight days after the onset of pneumonia The left lung where the process began is honeycombed with large rarefied areas in one of which a fluid level can be seen There is infiltration of the right upper lobe with a cavity at the level of the third rib The patient raised 300 to 500 cc of sputum at about this time and had intermittent high fever but recovery followed two weeks later (Reimann H A The Pneumonias W B Saunders Co 1938)

trauma or obstruction begins a few days to several weeks after the primary episode The abscess may be unsuspected until it ruptures into a bronchus or is discovered by roentgenography Usually high intermittent fever is present there is prostration toxemia cough and expectoration The sputum may vary in amount from a few cubic centimeters to a liter It is purulent perhaps blood tinged and settles into several layers or occasionally it may be chocolate colored from the presence of old blood There may be no odor or it may be offensive from putrefactive changes Shreds of lung tissue and myriads of bacteria are demonstrable by microscopic examination

The contents of an amebic abscess of the liver which has perforated the lung often may be recognized from the bitter taste of the bile and by its ochre-yellow color or anchovy sauce appearance Microscopic examination of such sputum reveals bile acid crystals elastic tissue recognizable liver cells and occasionally amebas In favorable cases specifically treated recovery may take place after several weeks with complete healing More often the disease becomes chronic in spite of treatment with frequent exacerbations especially if drainage is blocked

In chronic abscess of the lung many of the systemic symptoms may disappear but cough and copious sputum persist for months or years Hemorrhages may occur Frequent exacerbations and remissions are common Dyspnea cyanosis cachexia pyemia brain abscess mediastinitis empyema and amyloid disease may follow

Physical Signs—The physical signs of lung abscess as a rule are not helpful especially if the abscess is small or deeply located An abscess near the surface may occasionally be detected by a slight dulness and changes in the breath and voice sounds Tympany amphoric or cavernous breathing and egophony are absent unless cavitation occurs and the abscess is evacuated Rales may be present early before cavitation begins or afterward in the presence of pneumonitis There may be slight cyanosis clubbed fingers and dyspnea In chronic cases the physical signs depend upon the amount of fibrous tissue formed and on the character of the complications

Diagnosis—The diagnosis may be first indicated by the expectoration of foul pus following a brief illness as already described Physical examination may aid but often definite physical signs are lacking Exploratory puncture for diagnosis is contraindicated because of the danger of spreading the infection Bacteriologic examination of sputum should always be made since in some cases a single variety of organism may be involved and specific treatment indicated

Bronchoscopy should be performed in cases of obscure etiology to detect a possible foreign body or tumor



Fig 93—A large well-drained thick walled single cavity in the left upper lobe surrounded by a narrow area of peripneumonitis Another roentgenogram two weeks later showed enlargement of the cavity with spread to the other lung but a third plate one month later showed great improvement

The abscess developed twelve days after tonsillectomy Treatment consisted of bronchoscopic drainage

Roentgenography is of great value in diagnosis and without it many lung abscesses would not be diagnosed especially in those who recover Films should be made at frequent intervals both anteroposteriorly and laterally to locate the abscess follow its progress and to detect any lesions behind the heart and the domes of the diaphragm Early in the disease there may be found a homogeneous density (Fig 91) which after a few days may show rarefaction in the center and still later cavitation (Figs 92 and 93) with or without a fluid level The periphery of the shadow is soft and fuses

with the surrounding tissue unless pneumonitis is present If *the cavity is full of* pus or necrotic tissue and without drainage typical rarefaction is of course, absent The lesions may disappear without trace or they may leave permanent scars

The intrapulmonary injection of radiopaque iodized oil is often helpful in mapping out diseased areas and in differentiating the disease from bronchiectasis but when there are large amounts of sputum the oil may fail to reach the abscess In chronic cases cavitation with a fluid level is more *sharply outlined due to encapsulation* with fibrous tissue and perhaps with bone formation Extensive fibrosis and distortion are common Roentgenograms greatly aid in making the decision for surgical intervention

In *differential diagnosis* pulmonary tuberculosis bronchiectasis pneumonia foreign body in the bronchus lung tumors perforating empyema amebiasis and cysts are of especial *importance* A history of eating peanuts has aided in diagnosis in several of my patients who were unaware of having aspirated one Foreign body abscess should be suspected in small children and in the aged especially after operation on the nose and throat

Specific *infections like tuberculosis Bacillus friedländer* infection fungus infections and amebiasis can be diagnosed by identifying the causative organism The differentiation *from bronchiectasis and massive ne*crosis may be difficult or clinically impossible Many elderly patients who die from lung abscess also have pulmonary cancer In cancer the following symptoms are helpful in diagnosis edema of the arm or face displacement of the heart paralysis of the recurrent laryngeal or phrenic nerve symptoms of involvement of the brachial plexus or the development of Horner s syndrome rapid reaccumulation *of pleural fluid* if tapped and bronchial stenosis as discovered by roentgenography or bronchoscopy Malignancy should be particularly suspected in persons more than forty five years of age but it *may* occur at any age Exploratory thoracotomy may be indicated for diagnosis

Prognosis—Many lung abscesses heal spontaneously (Figs 92 and 93); others respond to no treatment whatsoever The *prognosis always* is better in persons otherwise healthy and less than forty years of age and especially in children Patients may recover spontaneously from abscesses which follow pneumonia and from those due to *metastatic or postoperative infection* but authorities differ greatly as to the frequency with which this occurs Some claim that recovery is spontaneous in 7 per cent others in 60 per cent of their cases The outlook is *most favorable when the abscess opens* into the bronchus and drains freely Such may heal and leave no scar Empyema following the rupture of superficial abscesses into the pleural cavity may be cured by surgical drainage In untreated fatal cases, if not a feature of septicemia there is an *average life expectancy of three years* during which time many of the symptoms present are those of the secondary pulmonary fibrosis and bronchiectasis Lung abscesses secondary to amebic liver abscesses have a *fair prognosis if specific treatment* is used Embolic abscesses which arise from a septicemia usually run a rapidly fatal course

Treatment—The best results of treatment are obtained by applying general rules to the circumstances of each case individually The chief factors governing treat*ment are* (1) *the underlying* cause of the abscess (2) the duration of the abscess (3) the general condition of the patient (4) the site and extent of the lesion (5) *the specific etiologic agent* and (6) the presence of complications in the lung and pleura

Acute abscess is best treated without surgery unless the course of the disease is stationary or if after a month or more the patient is losing ground There is usually a tendency to spontaneous healing and in more than 60 per cent of cases rest or postural treatment will suffice

During the acute stage of pulmonary abscess rest in bed in the open air and a nutritious diet are as *essential as in* pulmonary tuberculosis This sometimes is the only treatment necessary It is of greatest importance to remove the cause if one can be found In chronic cases supportive treatment is necessary with especial attention to maintaining suitable diet and preventing *anemia*

Drug therapy by mouth or administered intrabronchially is of very little value except for the treatment of amebic abscess (see page 843) Inhalations of vapor of compound tincture of benzoin and various preparations of creosote in steam serve only to deodorize or mask the unpleasant odors or taste There are no effective antiseptics Sulfanilamide or its compounds are of no value unless the hemolytic streptococcus or pneumococcus plays a role Arsphenamine has no place in the treatment since the spiral organisms often present are not believed to be of primary etiologic importance and even if they were there is no evidence to show a specific effect of the drug upon them Vaccine treatment and treatment with roentgen rays have not been helpful Patients should not be poisoned with potassium iodide because of the presence of yeasts or fungi in the sputum They are usually secondary invaders growing in necrotic tissue

After the abscess has ruptured into a bronchus but not while the condition is still acute postural drainage repeated three or four times a day should be practiced Abscesses of six months duration or longer rarely heal spontaneously For such drainage through the bronchoscope is sometimes satisfactory but only if drainage is obstructed by thick exudate foreign body or granulomatous tissue or edema of the bronchial mucous membrane This may be the only form of nonsurgical drainage possible when the abscess is surrounded by an extensive zone of pneumonitis or a thick fibrous wall

Collapse of the lung by artificial pneumothorax has been used with some success in the treatment of pyogenic abscesses but only when they are deeply located This procedure however by kinking the bronchus may hinder drainage and always makes difficult or impossible a later more radical operation It is not suitable for routine use Many therefore prefer phrenicectomy or phrenicotomy Some authorities would not collapse the lung under any circumstances since this procedure has been followed occasionally by rupture of the abscess into the pleural cavity with the production of severe and sometimes fatal empyema

Radical surgery should be considered if the abscess is superficial and if after three to six weeks (some recommend even three months) of medical treatment there has been little improvement, if all pleural pain has ceased and if the abscess as seen in the roentgenogram has become well demarcated Earlier operation is recommended if there is considerable cough with nausea anorexia insomnia and rapid loss of weight and strength, but in general it should not be attempted while the patient is critically ill for at that stage the postoperative mortality is high The fatality rate may be as low as 10 per cent if the operation is preceded by a period of a few weeks of rest in bed with postural drainage An operation not later than at the end of two months may forestall many complications and also lessen the degree of fibrosis and bronchiectasis likely to follow The operation should if possible be done under local anesthesia and free, dependent open drainage obtained If the patient s condition permits a two stage drainage operation is preferable Late surgical drainage that is two to seven years after the onset at which time a dense fibrous wall will have formed around the abscess is much less successful than earlier operations and the mortality is high For chronic abscesses lobectomy and pneumonectomy are being used with more and more success The relative merits of operative procedures are critically reviewed by Maxwell

Prevention —The recent knowledge accumulated concerning the frequency of lung abscess after certain types of operations should lead to the adoption of measures to reduce the hazard of this complication to the utmost

Every precaution should be taken at all periods of life to prevent the aspiration of foreign bodies both in consciousness and especially during coma from any cause

Hobart A Reimann

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MASSIVE NECROSIS OF THE LUNG

(*Gangrene of the Lung*)

Occurrence—Primary necrosis of the lung or death en masse with putrefaction of lung tissue is a rare condition unless one includes certain lung abscesses Secondary necrosis occasionally develops in the walls of tuberculous cavities pyogenic abscesses, and bronchiectatic dilatations and in areas of pulmonary infarction and pneumonic consolidation

Etiology—The organisms responsible for necrosis have not with certainty been identified The presence within the necrotic tissues of the fusospirochetal micro organisms is not rare and because of them attention has been called to the association of pulmonary necrosis with dental caries pyorrhea alveolaris and especially with operations on the mouth Spirochetes however often are absent, but it is generally admitted that anaerobic organisms are important

Pulmonary necrosis sometimes develops in the absence of all other recognizable causes Marked debility however, seems to be an almost necessary predisposing factor, since *so many patients who develop it are diabetic* insane or convalescing from protracted fever Necrosis rarely follows primary pneumonia *but more often it follows aspiration* pneumonia it is the rule when a cancer of the esophagus perforates into the lungs The walls of a bronchiectatic cavity especially if the dilatation is due to pressure on its bronchus not infrequently becomes necrotic Gangrene may develop in a septic infarct Necrosis of the lung and abscess of the brain are frequently associated conditions

Pathology—Diffuse pulmonary necrosis may convert the greater part of one lobe into a greenish black mass in the center of which forms a ragged cavity filled with foul smelling material

In the circumscribed form the focus may be single or multiple the lower lobe is more commonly affected than the upper and the peripheral more than the central portions of the lung If due to an embolus the plugged artery *can sometimes be found* Gangrenous areas at first are greenish brown in color and firm but soon break down and form cavities Each area is surrounded by a zone of consolidation this in turn by one of deep congestion on the periphery of which is a halo of intense edema which is sharply marked off from the surrounding normal tissue These areas show little or no tendency to spread When the liquefaction of the tissue is rapid, the walls of the contained blood vessels may rupture before they become closed by thrombosis with profuse hemorrhages the result Embolic processes not infrequently start from these areas The liquefied tissue usually excites an intense bronchitis Pyopneumothorax may develop

Symptoms and Course—The presence of necrosis in such pulmonary lesions as those *of pneumonia abscess infarction usually* is unmistakable since both the odor of the breath and that of the sputum are characteristic and may permeate the entire house but localized areas of necrosis which have no free communication with bronchi may remain quite unsuspected during life The same is true of the areas of necrosis seen in some cases of diabetes mellitus even when they have outlets for they may be odorless The fetor of gangrenous sputum usually is much more offensive than is that of fetid *bronchitis, bronchiectasis or abscess of the* lung nevertheless it alone is insufficient for diagnosis The sputum usually is profuse and, *if collected in a tall glass* cylinder separates into three or more layers the top thick and frothy, the middle thin liquid and sometimes with a greenish or a brownish tint and a greenish brown sediment in which are shreds of decomposing lung tissue Blood often is present in the sputum but as a rule it is much altered The sputum microscopically contains elastic fibers in abundance granular matter pigment grains fatty crystals and micro organisms

Among the general symptoms of diffuse necrosis are fever usually of moderate grade rapid pulse and prostration which usually progresses until the patient dies Circumscribed areas develop more gradually and show *little tendency to spread* Patients with such lesions generally die later of exhaustion Profuse often fatal hemorrhages are not rare Some patients however recover even those who have expectorated large fragments of lung tissue In such cases the fetor of the breath lessens the sputum becomes more and more purulent and dimin

ishes in amount and the clinical picture improves

In cases of necrosis the physical signs of intense bronchitis are often present also those of cavity if the latter lies in a superficial location Limited circumscribed gangrenous areas difficult to detect by physical diagnosis *may be discovered by roentgenography*

Prognosis —Massive pulmonary necrosis *usually is a terminal condition*

Treatment —The treatment of necrosis of the lung is on the whole very unsatisfactory and consists chiefly of regulation of the diet personal *hygiene to lessen the odor and* careful nursing Necrosis associated with *Bacillus welchii* should be treated early with specific antisera which should be used in large quantities It is possible that sulfanilamide may prove effective but no reports of its trial for gas bacillus infection of the lung are available

Among the various measures attempted to mask the odor of the breath and sputum are an intratracheal spray of weak dilutions of phenol and inhalations of vaporized creosote compounds They are usually unsatisfactory The patient may wear over the mouth and nose an inhaler containing solutions of phenol or guaiacol The following solution injected *intravenously every other* day is often helpful sodium iodide 0 15 Gm (2½ grains) guaiacol 0.3 Gm (5 grains) alcohol 2 cc (*¼ drachm*) *distilled water* 20 cc (⅔ ounce) The sputum cup may be deodorized by a 1.3 per cent solution of chloral hydrate and the mouth rinsed with a weaker solution of the same drug If the patient's condition is good and the necrotic region *is superficial and well localized* surgical intervention is desirable In cases of unilateral necrosis artificial pneumothorax has been recommended by some and phrenicectomy by others Many object to these treatments on the ground that they interfere with the drainage of the cavity Certainly they should not be employed if the lesion is near the pleura or if there is free fluid in the pleural or pericardial sac

HOBART A REIMANN

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PULMONARY FIBROSIS

Etiology and Occurrence —Pulmonary fibrosis is the result of pathologic processes in which the substitution of fibrous tissue for the normal lung parenchyma takes place The changes may be local and limited to a relatively small area or diffuse involving either one or both lungs *The fibrosis may* be limited chiefly to the bronchi or bronchioles (bronchiolitis obliterans) and blood *vessels (vascular fibrosis pulmonary arterio* sclerosis page 849) the interlobar septums the alveolar walls (chronic interstitial pneumonia) the pleura or it may involve several *or all of these areas (pulmonary cirrhosis* pneumonoconiosis page 853)

Local fibrous changes also surround or replace pulmonary tumors areas of atelectasis infarcts pneumonia abscesses bronchiectatic cavities masses of pigment gummata, irradiated areas (Fig 94) and hydatid cysts and form a wall around encapsulated and inspissated empyemas Scar tissue which produces pleural thickening may extend throughout the lung Fibrous changes not only surround aneurysms and new growths but also appear in the regions of the lung *which are compressed by these conditions*

Local fibrosis is the essential element in the healing of tuberculosis It is therefore *most often found in the apexes of the lungs* but other causes may also be operative there In cases of chronic pulmonary tuberculosis *in which the tendency to heal keeps* pace with the process of necrosis but does not surpass it the most of one or both lungs may in the course of years be converted into a dense mass made up chiefly of fibrous tissue

Diffuse fibrosis may be the result of chronic disturbances (Fig 95) of the lungs bronchi or pleura It may be a rare sequel after pneumococcic lobar pneumonia in which the normal process of resolution fails and the exudate is replaced by fibrous tissue A number of filtrable viruses particularly influenza virus attack the interstitial tissues of the lung which may favor the subsequent development of fibrosis

Diffuse pulmonary fibrosis may develop in some cases of long standing chronic passive congestion emphysema and asthma Fibrosis follows the inhalation for years of certain dusts the particles of which stored

in the interlobular lymphoid tissue become walled in by fibrous tissue (see Pneumonoconiosis page 853) These changes are especially marked at the hilum areas and bases of the lungs Fungous infections of the lung radiation pneumonitis and the inhalation of irritating gases may result in fibrosis

In about 25 per cent of all cases of pulmonary fibrosis however no definite cause is discovered for its presence either during life or at necropsy

Symptoms and Course—Pulmonary fibrosis is essentially a chronic disease extending over many years Its symptoms vary

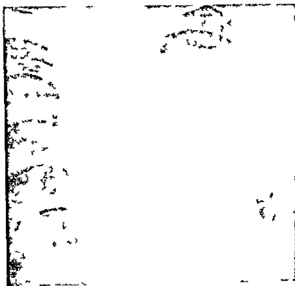


Fig 94—Localized pulmonary fibrosis after intensive radiation given for neoplastic metastasis in the lung Fibrosis was found at necropsy in the dense area in the left lung (Courtesy of Dr L G Rigler)

considerably according to the stage and extent of the process The most common are chronic cough cyanosis and slight shortness of breath If bronchiectasis develops there is paroxysmal cough abundant sometimes fetid expectoration and occasionally hemoptysis Some cases of fibroid phthisis can be distinguished from nontuberculous pulmonary fibrosis only by the signs in the former of a cavity at one apex or by the presence of tubercle bacilli in the sputum often the final diagnosis can be made only at necropsy Many patients with fibroid phthisis when once the condition has become established have shortness of breath only on exertion are able to do light work and enjoy fairly good health In advanced cases hypertrophy of the right ventricle dilation of the pulmonary conus (cor pulmonale) and so called pulmonary hypertension (page 849) result from the increase in peripheral resistance brought about by a reduction of the capillary bed in the lungs Death occasionally is due to pulmonary hemorrhage or intercurrent infection but is



Fig 95—Diffuse pulmonary fibrosis in a woman of 36 who had had asthma for sixteen years Her complaint was progressive weakness dyspnea, asthma and slight pain in right upper quadrant Dusky cyanosis of the upper part of the body was first mistaken for hemochromatosis and for polycythemia The veins of the ocular fundi neck forearms and abdomen were greatly distended and the liver enlarged There were musical squeaks wheezes and rales in both lungs and constant dyspnea even at rest but no acropachy Erythrocytes 5 200 000 leukocytes 9 000 hemoglobin 105 per cent pulse rate average 100 respiratory rate 27 blood pressure 105/70 and there was slight fever

Roentgenogram shows numerous tents and depression of the diaphragm emphysema, thickening of the hilum increased bronchovascular markings enlarged cardiac pulmonic conus and diffuse fibrosis throughout especially dense in the midportion of both lungs

The cyanosis slight polycythemia, enlarged pulmonary conus and evidence of myocardial insufficiency suggest Ayerza s disease (p 850)

more commonly the result of gradual heart failure

Physical Signs—When the disease is unilateral and well established the affected side of the chest is retracted deformed and immobile the intercostal spaces are narrowed or obliterated the ribs may even overlap the shoulder is drawn down the muscles of the shoulder girdle are atrophied and there is scoliosis of the spine its concavity toward the lesion Litten's sign is absent

on the affected side The mediastinum is pulled toward the side involved

Mensuration of the affected side shows a decrease in its size and the tape demonstrates its limited expansion on inspiration The note on percussion varies it may be absolutely flat everywhere particularly at the base or apex but if the bronchi are large and sacculated the note in the axilla may be tympanitic or amphoric On the normal side the percussion note usually is hyperresonant and the breath sounds and tactile fremitus are exaggerated Cardiac murmurs are not uncommon particularly late in the disease after the right ventricle has begun to fail In some cases the chief symptoms from the first are cardiac in nature the evidence of gradual heart failure In bilateral disease the signs are those of chronic asthma with no outstanding characteristic signs Rales are not prominent unless heart failure or infection is present Many of the long bones especially those of the fingers may show pulmonary osteoarthropathy (acropachy)

Diagnosis —The diagnosis of pulmonary fibrosis is seldom difficult but in the absence of a clear history it may be impossible to say what the primary process was Tuberculosis may be hard to exclude as the cause yet even in long standing cases of phthisis tubercle bacilli usually are present in the sputum and there is often evidence of this disease in the other lung The roentgenogram is of great assistance in diagnosis (Figs 94 and 95)

Treatment —All those measures so useful in cases of pulmonary tuberculosis such as dry climate wholesome diet and cod liver oil are of value in the early stage of pulmonary fibrosis Any focal infections which might favor the progress of secondary processes should be eliminated Usually it is because of some intercurrent affection or for an aggravation of the cough that the patient seeks relief Nothing can be done for fibrosis once it has fully developed The patient should if possible live in a mild climate and avoid exposure to wet and cold Cardiac weakness is a common feature of this disease and should receive proper attention At times the putrefaction of the contents of the dilated bronchi is distressing and requires the same measures recommended for massive necrosis (page 847) For the disfiguring deformities of the chest which sometimes develop various gymnastic exercises have been suggested, especially those which immobilize the sound while inflating the diseased, pulmonary tissue Roentgen ray therapy is useless

Hobart A Reimann

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PULMONARY ARTERIOSCLEROSIS

(*Pulmonary Hypertension*)

According to some writers pulmonary arteriosclerosis and pulmonary hypertension are dependent upon each other and there is controversy as to which is cause and which is effect Obviously, a diagnosis of arteriosclerosis can only be proved at necropsy and there is no way of measuring the blood pressure in the pulmonary or lesser circulation The diagnosis is made by inference The signs and symptoms of both conditions however are apparently similar Pulmonary arteriosclerosis is classified into primary and secondary forms The cause of the rare primary form is unknown but in a few cases syphilis or rheumatic fever has been suspected The secondary form may follow numerous long standing hyperemic states such as accompany bronchiectasis tuberculosis congenital cardiac anomalies thoracic deformities emphysema asthma passive congestion from chronic cardiovascular disease or any other condition causing peripheral resistance in the pulmonary circulation In limited forms there is thickening of the intima and degeneration of the media of the pulmonary artery and partial or complete obliteration of its branches The arterioles and capillaries may be involved especially in the secondary form Pulmonary arteriosclerosis may of course be included in general systemic arteriosclerosis or may be a part of pulmonary fibrosis described in the preceding section

Symptoms —The condition is often unnoted clinically or mistaken for some other disease or masked by the primary disease

The chief symptoms are dyspnea vertigo, hemoptysis and precordial pain There is increased venous pressure accentuation of the second pulmonic sound, dilatation and hypertrophy of the right side of the heart, of the pulmonary conus and of the superficial veins also cyanosis enlargement of the liver, lowered renal function and infarction of the lungs Pulsation in the intercostal spaces, a bruit heard all over the chest and an up and down movement (dance) of the diaphragm are said to occur The absence of rales in the presence of an enlarged liver ascites and edema is also said to be of importance in diagnosis Cough with sputum is commonly present Characteristic changes are noted in roentgenograms of the chest (Figs 95 and 96) The condition may last for years and terminate in myocardial failure or by intercurrent infection The name *Ayerza s disease* is applied to the advanced stage when cyanosis and polycythemia are present (Fig 95) Giesbock s disease to some cases if there is cyanosis and hypertension, and still others are included in the Osler-Vaquez syndrome

The treatment is chiefly that for the primary condition if one is present otherwise it must be palliative Rest and inhalation of oxygen are temporarily useful Residence in an equable climate is desirable

HOBART A REIMANN

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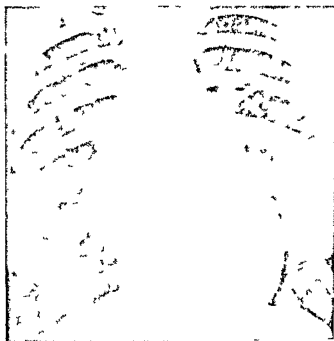


Fig 96—Pulmonary arteriosclerosis There is great enlargement of the pulmonary artery and its peripheral branches which were seen to pulsate under the fluoroscope There is also the characteristic enlargement of the right side of the heart (Courtesy of Dr L G Rigler)

RADIATION PLEUROPNEUMONITIS

High voltage roentgen therapy applied to the thorax for various purposes often causes pneumonitis and pleurisy with effusion The susceptibility of the lungs of different persons to roentgen rays varies considerably some are affected by small doses others tolerate massive doses If radiation is continued over an extended period as it often is for neoplasm pulmonary and pleural fibrosis develops

The milder forms of pneumonitis or pleuritis are symptomless and can be recognized only by roentgenograms In more severe forms symptoms resembling an acute in

fection of the lungs appear about a week after radiation Pleuritic pain dyspnea on exertion and dry cough are noted The symptoms usually disappear soon if no further radiation is given but in some instances the condition may result in permanent fibrosis

The diagnosis is made on the history symptoms and roentgenographic findings (Fig 94) There is no treatment except to prevent further injury from roentgen rays by proper shielding or directing of the rays

HOBART A REIMANN

CHEMICAL PNEUMONIA

Chemical pneumonia is the term applied to acute pulmonary lesions caused by the inhalation of irritating gases particularly chlorine bromine ammonia sulfur dioxide phosgene chlorpicrin lewisite mustard gas various acetates diethylphthalate and ethylene halides Gases inhaled in strong concentration may lead to sudden death from shock or to intense catarrhal inflammation pulmonary edema and asphyxia Less severe exposure results in a condition similar to that of the acute infectious pneumonias Bacterial invasion and pneumonia may follow Lung abscess necrosis bronchiectasis emphysema or fibrosis may result

The treatment for the severe forms is like that for shock for the mild form it is the same as for pneumonia (page 116)

HOBART A REIMANN

ALLERGIC PNEUMONIA

Transitory lung infiltration with eosinophilia (Loeffler s pneumonia) is believed to be the result of the reaction of sensitized lung tissue to an antigen Persons suffering from asthma allergic rhinitis and urticaria occasionally develop the signs and symptoms of a mild inflammation of the lung Slight fever cough with sputum and moderate leukocytosis with a high proportion of eosinophile cells are found The signs in the lungs may be minimal or absent but a massive infiltration may be seen in a roentgenogram The shadow may disappear in a few days

The condition is important because it may be mistaken for tuberculosis coccidioidomycosis or pulmonary ascariasis and because it can so often be prevented by removal of the offending sensitizing agent or relieved with epinephrine before secondary invasion by bacteria occurs

HOBART A. REIMANN

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NEW GROWTHS IN THE LUNGS

Among the new growths of the lungs may be mentioned carcinoma sarcoma the enlarged lymph nodes of Hodgkin s disease and the leukemias as representing the most common malignant forms and dermoid cysts adenoma chondroma osteoma neurofibroma and lipoma as benign growths

Benign growths may give no indication of their presence for years unless as they enlarge they press on important organs or give rise to secondary infections and ulceration or to obstruction of the air passages They are often discovered first by roentgenography or at necropsy

Malignant Growths —Carcinoma of the lung both primary and secondary or metastatic is the most important of the neoplastic diseases The secondary form occurs more often but both seem to be increasing in incidence It is a source of controversy whether the increase is apparent or real and much evidence favors both views Primary cancer of the lung occurs next in frequency to cancer of the gastro intestinal tract and causes from 5 to 10 per cent of deaths from cancer Of all cases 9 per cent develop between the ages of 21 and 40 and 72 per cent between 41 and 60 years

The *cause* of course is unknown but all factors are said to have one quality in common namely chronic irritation The irritation may be caused by chemical mechanical bacterial radioactive and perhaps thermal means (Simons) Some believe that chronic irritation plays no role

The majority of primary cancers arise from the bronchial epithelium a few from the bronchial mucous glands The right lung is more often involved than the left and the upper lobes more often than the lower Tumors of the larger bronchi may lead by occlusion to bronchiectasis atelectasis or

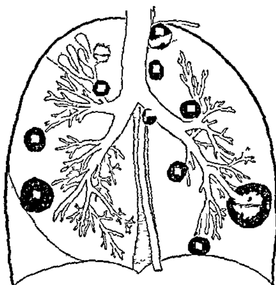


Fig 97—Illustrating the pathogenesis of symptoms and signs in primary carcinoma of the lung 1 Tumor near the pleura may produce pleurisy and serous or bloody pleural effusion 2 In this area a tumor may be silent for months 3 If a bronchus is occluded atelectasis and dilatation of the distal bronchi may occur with bronchiectasis pneumonitis or abscess formation 4 A tumor in the apex may cause erosion of a rib paralysis of the sympathetic trunk causing a Horner's syndrome pain in the arm and partial paralysis of the ulnar and median nerves by invading the first dorsal root of the brachial plexus and invasion of adjacent structures 5 Pressure here may cause paralysis of the recurrent laryngeal and phrenic nerves 6 Incomplete obstruction of a large bronchus often causes unilateral wheezing and may cause obstructive emphysema 7 Ulceration of the bronchial mucous membrane gives rise to blood streaked sputum or recurrent hemorrhages 8 Tumors may undergo central necrosis with abscess cavitation and bronchial fistula 9 Irritation of the diaphragmatic pleura may cause pain of typical phrenic nerve distribution 10 Invasion of the esophagus with obstruction or ulceration may occur (Churchill E D, in Christopher's Textbook of Surgery Ed 2 W B Saunders Co)

abscess but more often they leave the bronchus open Pleural effusion pneumonia abscess or gangrene, and purulent bronchitis commonly occur

Symptoms —Metastatic lung cancers usually develop in the interstitial tissues of the hilum and cause few symptoms unless by pressure they close one of the bronchi Primary neoplasms grow insidiously the first *indication often being given by extrathoracic metastasis* A few start acutely with dyspnea hemoptysis and pain but usually the symptoms and signs are not those of carcinoma alone but rather of its secondary effects (Fig 97) The symptoms resulting from these changes are those of *atelectasis* bronchiectasis obstruction or abscess These account for the following symptoms noted in order of frequency cough sputum pain in the chest dyspnea weakness and emaciation fever hemoptysis dilated thoracic or cervical veins and cyanosis Other less common symptoms are night sweats vomiting hoarseness and acropachy

Cough is the most common symptom and is usually accompanied by an ordinary mucoid or mucopurulent sputum Cough once started usually persists regardless of treatment Wheezing respiration may be heard Pain may be local or referred to the shoulder arm or epigastrium Dyspnea which may appear early or late occurs in 59 per cent of cases especially if pleural effusion is present Low fever is present at some time in about 50 per cent of cases Weakness is common and cachexia develops late in the disease Edema of the arm or face displacement of the heart paralysis of the recurrent laryngeal and phrenic nerves or the brachial plexus rapid reaccumulation of bloody pleural fluid if tapped, Horner's syndrome and evidence of bronchial stenosis are all important signs

The *physical signs* of pulmonary cancer often are indefinite, since the tumor is usually covered by a layer of normal pulmonary tissue Those most common are wheezing or bronchial breath sounds and unusually well heard voice sounds in the conduction of which these solid tumors greatly aid If however the tumor invades the pleural surface or ulcerates through the bronchial mucosa pleural effusion bronchiectasis or lung abscess may arise In cases with pleural effusion the heart may or may not be displaced

Primary cancers of the upper lobe early present certain almost pathognomonic physical signs almost complete flatness and a sense of resistance in the infraclavicular fossa and diminished or absent vesicular breath sounds but no tubular breathing no amphoric sounds and a few or no rales

The life expectancy in cases of primary

cancer of the lung varies from one and one half months to five years the average expectancy is nine months after the appearance of symptoms

Diagnosis —The possibility of the presence of a primary cancer of the lung should always be borne in mind when patients more than 40 years of age who before have been well prior to one year complain of any of the following symptoms loss of weight not easily accounted for the sudden appearance without evident cause of cough pain in the chest shortness of breath or hemoptysis dyspnea in the absence of cardiovascular disease or a severe persistent boring pain in the chest, not accompanied by a pleural rub or signs of aneurysm

Today about 50 per cent of all cancers of the lung are diagnosed clinically though in the great majority of instances the diagnosis is made too late for efficient treatment Twenty years ago only 5 per cent were recognized before necropsy The diagnosis should be made however in 90 per cent of cases if careful consideration be given to the history roentgenograms physical examination bronchoscopy biopsy of lymph nodes or of tissue removed through the bronchoscope and study of the cells of any pleural effusion present The possibility of cancer should be considered in all cases of lung abscess bronchiectasis recurrent or unresolved pneumonia empyema hemorrhagic pleurisy and suspected tuberculosis Against tuberculosis are the facts that a primary cancer usually begins at the root of the lung and the sputum contains no tubercle bacilli

Roentgenograms make the diagnosis in 93 per cent of all cases Primary films often show that the diaphragm is unusually high on one side but if artificial pneumothorax is produced the tumor may become evident A characteristic finding is a large dense shadow involving a part or the whole of a lobe with a hazy irregular edge and associated with shadows at or extending to the hilum Bronchoscopy with the removal of a piece of tissue often permits an early diagnosis but in many cases such a procedure is unnecessary

Treatment —In early cases in which there is no evidence of metastasis wide surgical excision (lobectomy or pneumonectomy) offers the best chance of cure Numerous successful operations have been reported with 'cures lasting from one to six years Bronchoscopic removal endobronchial diathermy cauterization and implantation of radon seeds have been reported to be successful in a few cases but the feasibility of such measures is limited to bronchogenic carcinomas Radiotherapy can only be considered as palliative at present Symptomatic treatment is all that can be given in advanced cases

HOBART A REIMANN

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PNEUMONOCONIOSIS

Definition —Pneumonoconiosis is a generic term comprising all the chronic fibrous reactions arising in the lung as a result of the prolonged inhalation of excessive quantities of injurious mineral dusts such as those of sand granite flint asbestos The term is used at times to describe pulmonary fibroses resulting from inhalations of dusts which are mixtures of substances in which the relative pathogenicity of each constituent is undetermined Many of the pneumonoconioses are scarcely to be considered as diseases since they may exist without producing symptoms or impairing physical efficiency as in the case of anthracosis chalicosis siderosis etc On the other hand dusts containing high concentrations of finely divided silica produce serious forms of pulmonary fibrosis of great medical and economic importance (silicosis) Admixture of carbon gypsum and hematite with silica in dust results in a modification of the reaction to silica retarding or inhibiting its noxious effects

The silicates vary greatly in pathogenicity —some are apparently inert others mildly pathogenic while still others may even exert a retarding effect upon the action of free silica Of the fibroses caused by silicates that due to asbestos (asbestosis) is probably the only one of importance though certain

investigators believe that some of the seri cites are pathogenic

As a rule the effects of inhalation of organic dusts are not included in the scope of the pneumonoconioses Such dusts may excite allergic reactions, they may introduce infection or result in local irritant or toxic actions

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SILICOSIS

Definition —Silicosis is a chronic condition of the lungs caused by inhalation of air containing finely divided particles of silica (SiO_2) in sufficient quantity and over a sufficient period of time to produce fibrous nodules *in the walls of the alveoli which are* readily recognizable in roentgenographs of the chest and in pathologic specimens Clinically the process is recognizable as a disease only in its advanced stages either by increased dyspnea on exertion or by the symptoms of tuberculosis to which it predisposes

Etiology —Silica is widely distributed in nature since it makes up a large part of the rocks and minerals which form the earth's crust It occurs free as SiO_2 and combined in the forms of silicates Quartz which is one of the most common forms of free silica occurs abundantly in granite and other rocks In consequence of this one might expect a high incidence of silicosis among workers in mines and *tunnels and in stone* cutters There are however a great number of other industrial processes in which workers may be exposed to dust containing considerable amounts of free silica Among these are listed the manufacture and use of abrasives sandblasting chipping buffing of metals metallurgic processes ceramic manufacturing glass making enameling and the molding of metals In 1930 it was estimated that more than a million industrial workers were potentially exposed to a silicosis hazard and that half of this number were exposed to truly dangerous quantities of airborne silica

Knowledge concerning the pathogenic effects of free silica in dust has come from several sources From the South African gold mines *from* the granite industry at Barre Vermont from the anthracite mines in Pennsylvania, from the gold mines of Ontario from the lead mines and sewer tunnels of New South Wales have come reports of long continued studies of dust conditions and their effect upon the workers in these industries Methods have been devised for counting dust listing the number of particles the distribution of their sizes and their composition These data are correlated with the health records of the workers, including their death rate from tuberculosis, and with the incidence of pneumonoconiosis as revealed by x ray survey

Another important source of knowledge concerning the injurious effects of dust is the work of the Saranac Lake Laboratory under the direction of Dr Leroy U Gardner who employs a technic in which animals *are kept in dusts of known concentration* for long periods of time so that the pathologic changes produced in their lungs may be observed From studies of this kind it appears that the relative dangerousness of dusts is roughly proportional to the concentration of free silica in the different varieties Other constituents of the dust are either inert or exert a modifying effect upon the reaction of the lungs to the free silica

The size of the particles is very important It is doubtful whether particles larger than 10 microns enter the finer air passages The greatest danger therefore lies in particles less than 10 microns and it is probable that the most dangerous size is that less than 3 *microns There are several reasons for this* The larger particles settle out of the atmosphere more quickly than do finely divided particles Also the injurious effect of silica is believed to be exerted after partial solution in other words its injurious effect is chemical rather than mechanical Since the smaller the particle the greater is the relation of surface to mass it is obvious why the smaller particles go more readily into solution

The most common method employed for the enumeration of particles of dust in air is the so called light field method by means of which it is possible to enumerate only particles more than 1 5 microns *in size* Recently a dark field method has been introduced which reveals a much larger number of particles less than 1 5 microns There is still much to be learned about the patho

genic aspects of these very minute particles since dark field counting is not yet standardized or generally employed

Donald Cummings of the Saranac Laboratory has summarized the present available data in regard to permissible dust concentrations Information from field studies in various parts of the world indicates that a normal man might work in pure crystalline silica dust for many years without impairing his health provided the concentration did not exceed 5 000 000 particles per cubic foot of air as determined by the light field counting method This has been called by Cummings the primary threshold The duration of exposure is of course a most important factor The rate at which silicosis develops under the same conditions varies with different persons In general it may be said that in individuals working in dust containing 5 000 000 particles of pure silica per cubic foot it would require from five to twenty years for the development of demonstrable silicosis The rate of development however does not appear to vary directly with the concentration of silica but increases slowly with elevations of the dust concentration up to a certain level at which a marked acceleration is noted Concentrations of dust in which there are more than 100 000 000 particles per cubic foot of air are extremely hazardous and this has been called by Cummings the secondary threshold" a value above which silicosis might be expected to develop with great rapidity Under such conditions nodular fibrosis might occur in as short a time as two years As a general rule from fifteen to twenty years working exposure to 15 000 000 or 20 000 000 particles of pure crystalline silica are required to produce demonstrable silicosis The Code of the state of Wisconsin provides that a maximum permissible concentration of dust is 15 000 000 particles containing not more than 35 per cent free silica and further provides that as the percentage of silica increases the permissible concentration must be proportionately decreased Tentative proposals have recently been made in New York State to define the permissible limits of dust during rock drilling The limits proposed range from 50 000 000 particles with 5 per cent free silica to 5 000 000 particles when more than 40 per cent is silica

Predisposing Causes—Reports from many parts of the world indicate that all races are susceptible Sex is not a factor—women develop the disease when exposed to the same conditions as men The age factor is very difficult to evaluate Surveys indicate that the incidence of silicosis is higher among young miners if the dust concentrations are high and higher among old miners when the dust concentrations are low These deductions however probably relate to the rapidity of labor turnover, rather than to an effect of age upon susceptibility to the disease Among predisposing causes, past and present respiratory infections are of great importance particularly those of the nasal sinuses Emphysema old pleurisies pneumonia and bronchitis are of importance in so far as they impair the dust removal mechanism of the lung The efficiency of the filtering mechanism of the nose appears to play an important role Some observers believe that mouth breathers are more susceptible than those with normal nasal passages The fact remains however that individual variations in susceptibility are poorly understood

Silicosis and Tuberculosis—In England the tuberculosis rate is higher among workers in dusty trades being three to ten times as high as the rate for all occupied and retired males Gardner has made the statement that At least 75 per cent of the human beings who develop silicosis die of tuberculosis which may make its appearance at any stage of the disease Such a statement however requires some qualification In anthracosilicosis and siderosilicosis of coal and iron miners the action of silica is somewhat modified the disease requires a longer time to produce disability and the incidence of active tuberculosis is less than in the case of unmodified silicosis

Modifying Factors—Apart from the modifying effect of coal dust and iron ore on the reaction to silica there is increasing evidence that other dust constituents are not entirely inert In a recent study of the gypsum industry Gardner has found evidence of a protective action of gypsum dust when it is mixed with silica Surveys of the cement industry have revealed a very low incidence of silicosis among the workers This has been taken by some to mean that there is a protective substance but it seems

more likely that the low incidence of silicosis is due to the small amount of free silica in cement dust Rapidly developing silicosis in the abrasive soap industry has been attributed to the accelerating effect of alkali This conclusion should be accepted with reservations, since it is also possible that the rapid development is due to an extraordinary proportion of particles of silica less than 0.5 micron in size the enumeration of which is not possible by the light field method

Morbid Anatomy—For purposes of description it is important to distinguish between the lesions of simple silicosis and silicosis with infection In *simple silicosis* the *essential lesion is the silicotic nodule* Typical nodules are 2 to 5 mm in diameter and are scattered more or less uniformly throughout the parenchyma of the lung under the pleura and in the nodes at the hilum They are avascular laminated fibrous whorls and when disseminated are usually situated at the entrance to a lobule They punctuate the perivascular lymphatic pathways between the alveoli and the hilum and between the alveoli and the pleura at the periphery of the lung There is frequently associated a perilymphatic fibrosis The alveoli may be thick walled and dilated The lymph nodes at the root of the lung are usually fibrosed and in their periphery may show typical laminated whorls As the process advances these minute miliary nodules may become agglomerated and ultimately may form dense fibrous rubbery masses of tissue replacing considerable numbers of lobules As fibrosis and atelectasis progress in the more fibrous portion of the lung the remaining portions may undergo considerable emphysematous change often with the formation of large blebs The pleura usually shows thickening and is frequently adherent

In the advanced forms with dense fibrosis and emphysema hypertrophy of the right ventricle is often observed associated with some tendency to dilatation of the pulmonary conus

Silicosis with Infection—The most important infection associated with silicosis is tuberculosis which may have antedated the silicosis in a latent apical focus or which may develop simultaneously with it or may arise from an exogenous source at any time during the course of silicosis The anatomic findings vary in accordance with the above possibilities

Tuberculosis in silicosis tends to be chronic The character of the reaction consists in formation of granulation tissue and scar Caseation and cavitation are late manifestations as a rule The tubercle bacilli are frequently very difficult to detect, either by staining or by inoculation

All the usual manifestations of tuberculosis may occur and the tuberculous infection may be extensive enough at times to obscure the underlying silicosis The combination frequently presents the picture of an organizing pneumonic area about the silica nodule which thus appears larger and less sharply circumscribed than in simple silicosis The coalescence of such nodules leads to larger dense fibrotic masses

Modified Silicosis—Nonsilicious dusts such as coal, emery, carborundum gypsum and iron produce collections of phagocytes in alveoli without thickening of the adjacent wall They may accumulate slowly in the lymph nodes and may be deposited about the lymphatics under the pleura and throughout the lung

In anthracosilicosis and siderosilicosis one finds perilymphatic fibrosis The greater the free silica admixture with coal or hematite the more hyalinization is seen If the free silica in dust is high nodular fibrosis is found

Symptoms—Simple silicosis may progress to advanced stages with no symptoms other than a tendency to shortness of breath This is noted at first on moderate exertion but as the disease progresses it may occur on less and less severe exertion It is not accompanied by orthopnea unless asthmatic paroxysms intervene The occurrence of orthopnea suggests an associated cardiac condition Riddell has pointed out that if severe dyspnea is produced by effort in two patients one with silicosis and one with heart disease the silicotic will be able to lie flat immediately after and the cardiac patient will not

Cough with uncomplicated silicosis is not a prominent symptom When it occurs it is noted chiefly in the morning and it is either dry or very slightly productive of mucoid

sputum Cough may occur while actually working in dust due to irritation of the nose and throat without reference to the existence of silicosis Men who have worked for a day in dust usually expel dust-discolored sputum on the following morning

When cough is a prominent symptom it is almost sure to denote complicating infection and in such cases it is usually more or less productive Even when tuberculosis is present tubercle bacilli are difficult to find in the sputum unless cavitation has occurred and this is usually a late phenomenon The fibroid tuberculosis most frequently accompanying silicosis may not be characterized by much fever or night sweats tachycardia or weight loss This is not an invariable rule but its frequent occurrence gives the impression that the silicotic fibrosis retards the symptoms of tuberculous activity

The physical diagnosis of simple uncomplicated silicosis is practically impossible The physical signs in simple silicosis are those of emphysema hyperresonance on percussion diminished intensity of breath sounds with prolongation of low pitched expiration Occasional rhonchi and fine and scattered medium coarse rales are heard in the interscapular regions and bases When signs other than these are elicited they are indications of a complicating infection rather than of the underlying silicosis One is repeatedly surprised by the great discrepancy between physical signs and the extensive pulmonary disease revealed by roentgenographs

In simple silicosis the circumferential expansion of the chest is usually diminished while good excursions of the diaphragm may persist In advanced cases with dense fibrosis and emphysema the diaphragmatic excursion is reduced When active infection is present expansion is impaired more than the extent of the lesions as revealed in roentgenographs would lead one to expect

Pathologic Physiology—The vital capacity of the lungs is a good measure of expansile capacity In estimating normality of vital capacity the West formula based upon surface area is most unsatisfactory Hurtado has found a better formula for prediction based upon measurements of roentgenographs of the chest made at full inspiration

The total pulmonary capacity (vital capacity plus residual air) tends to be reduced in proportion to the extent of the fibrosis The vital capacity is less than normal and the residual air is greater (when measured by the technic of Christie) In advanced cases the accuracy of the measurement of residual air may be open to question However when large values for residual air are observed there is severe functional impairment When the residual air exceeds 40 per cent of the total capacity the saturation of the arterial blood with oxygen is usually found to be less than normal

When patients with silicosis perform muscular work the volume of air expired per minutes is greater than in the case of normal men performing the same work Their breathing is more rapid and more shallow

The range of ventilation per minute found when normal men perform measured amounts of work (from 200 to 800 Kg m per minute) while riding a bicycle ergometer has been fairly well established When silicotics perform similar amounts of work the comparison of the ratio of ventilation to vital capacity with that of normals gives an index of the tendency to dyspnea

The maximal ventilation which an individual can attain may be estimated from the vital capacity on the assumption that 42 per cent of the vital capacity is used in each respiration thirty seven times a minute The pulmonary reserve is the difference between the actual ventilation per minute and the maximal When patients with silicosis perform measured amounts of work the ventilation per minute comprises a higher percentage of their maximal capacity than in the case of normal men performing the same work Thus their pulmonary reserve is less than normal for two reasons the minute ventilation is excessive and the maximal ventilation is limited in proportion as the vital capacity is reduced

The behavior of the pulmonary ventilation in silicosis is of precisely the same character as that observed by Harrison in heart disease In both instances it seems probable that interstitial changes in the lungs have

resulted in disturbances in the Hering Breuer reflexes

In advanced cases of silicosis with extensive fibrosis and emphysema hypertrophy of the right heart and dilatation of the pulmonary conus may be observed This phenomenon is best explained on the assumption that the capillary bed of the lungs has been reduced sufficiently to increase the peripheral resistance in the lesser circuit In about half the cases in which this *cor pulmonale* is found the electrocardiogram reveals right axis deviation and abnormality of T waves or S T intervals in leads II and III

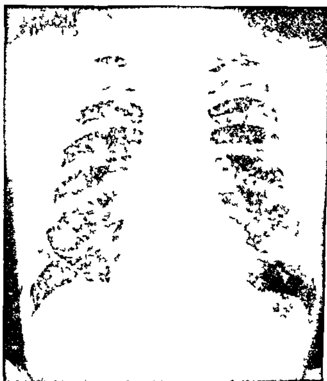


Fig 98—Silicosis showing beginning agglomeration in the left lower lobe with resulting secondary emphysema (Dark area just above left leaf of diaphragm)

Diagnosis—The two essentials to a diagnosis of silicosis are an accurate occupational history and characteristic roentgenographic findings The occupational history should cover all occupations in which the patient has been engaged and the duration of employment in each In connection with those occupations which are dusty as much information as possible should be obtained as to the amount and character of the dust and the extent to which protective devices were used

The roentgenographic findings have certain characteristics which, when taken with a reliable occupational history and the clinical findings warrant making a probable diagnosis of silicosis The roentgenograph alone cannot decide the diagnosis since there are a number of conditions which may give similar appearances

In roentgenographs of the lungs in simple silicosis there are seen discrete round shadows not exceeding 5 to 6 mm in diameter having clear cut borders They are fairly uniformly distributed in each lung The visualization of the process is greatly enhanced by stereoscopic viewing of the roentgenographs In addition to these appearances enlargement of the shadows of the tracheobronchial nodes is noted

In infective silicosis in addition to the picture of simple silicosis the following changes may be seen localized discrete densities mottling in which the shadows vary in size and have ill defined borders soft nodulation in which the nodules have fuzzy borders with irregularity in distribution

In advanced cases massive dense shadows appear with surrounding portions of increased radiotranslucency caused by dense

fibrosis and adjacent emphysema Frequently seen also are evidences of pleural thickening and adhesion and tenting" of the diaphragm

The diagnosis of silicosis is impossible before the discovery of shadows of silicotic nodules Before this stage is reached a positive or even probable diagnosis cannot be made Developing silicosis may be suspected from the observation of serial roentgenographs showing progressive changes when occupation is known to involve a dust hazard but the diagnosis should not be made until nodular shadows are seen

Differential diagnosis involves the exclusion of other causes which may give similar roentgenographic appearances Simple diffuse nodular silicosis must be differentiated from miliary tuberculosis by the absence of fever tachycardia and wasting which characterize the latter Similarly metastatic tumors the mycoses and tularemia must be excluded

The finding of silica particles in the sputum is of little value in diagnosis unless the patient has been excluded from all contact with silicious dusts for some time

Prophylaxis of silicosis is one of the major concerns of the industrial physician in charge of workers in dusty trades Systematic studies should be made of the air suspended dusts at breathing levels of the workers When excessive dust concentrations are found and especially when the percentage of free silica is high cooperation of managerial and engineering departments must be enlisted to improve ventilation and remove dust

Many devices are now available for the protection of workers in rockdrilling sand blasting chipping and grinding and foundry work These protections are constantly being improved

It is important not only to see that adequate devices are provided but to insist upon their use and frequent inspection in order to keep them in usable condition

Periodic examination of workers exposed to dangerous dusts is highly important The exclusion of men with open tuberculosis is a great protection to other workers Serial roentgenographs should be made at intervals

Treatment —There is no specific treatment for simple silicosis Infective silicosis should be dealt with as tuberculosis The *prognosis* in many cases of silicosis with tuberculosis is not as hopeless as many have assumed it to be When tuberculosis occurs with a modified silicosis in an iron or coal miner, or a foundry worker suitable treatment may cause arrest of the disease

Among copper and gold miners sand blasters and granite cutters the outlook is serious if tuberculosis develops It is important however for the patient to receive the same treatment as he would if silicosis were not present

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EMPHYSEMA

Definition —Emphysema is a condition in which the alveoli of the lungs become distended or ruptured The term is also applied to a condition in which there is air in the subcutaneous and interstitial tissues and which has nothing in common with the other form except the name

The disease was described by Floyer and by Morgagni in the eighteenth century but not until publication of the classic description of Laënnec and of Jenner was its clinical significance or its pathology well understood

Etiology —*Obstruction of the Air Passages* —Emphysema may arise from any condition which causes distention of the lungs and is particularly favored by circumstances which allow greater interference with expiration than with inspiration Experimentally great distention of the lungs can be produced without damage if the pressure is quickly released the elasticity of the normal lung causing it to return to its usual position If even moderate distention be maintained however changes in the lung become permanent with disturbance of local circulation and loss of elasticity In the distended position of the lung anything which increases

intrapulmonary pressure such as coughing or straining may advance the process

Clinically acute emphysema may in certain rare cases be caused by a *valvelike obstruction* which admits some air without allowing it to escape A flapping diphtheritic membrane or the tenacious mucous exudate of chronic bronchitis acts in this way Such true valvular action, although most effective in producing rapid distention is by no means necessary The very nature of the respiratory mechanism enables any partial obstruction to produce emphysema Inspiration is accomplished by powerful contraction of the diaphragm and the intercostal muscles Expiration under ordinary circumstances is passive and even when aided by the accessory muscles is not so forceful as inspiration Consequently in inspiration air passes the obstruction with comparative ease while expiration is prolonged difficult and often incomplete A gradual distention of the lungs results *Asthma chronic bronchitis and* whooping cough are frequent causes of emphysema It may also arise from tumors in the mediastinum or from partial obstruction of the larynx

Changes in the Size and Shape of the Thorax—Because of the negative pressure in the pleural spaces the lungs tend to adapt themselves to the size of the thorax Thus in conditions such as Paget s disease and acromegaly which are characterized by bony overgrowth of the thorax stretching of the lungs sometimes of extreme degree *may occur as an entirely secondary phe*nomenon

In 1858 Freund advanced the theory that *many cases* of emphysema might be the result of a primary disease of the costal cartilages consisting of hyperplasia and premature ossification causing enlargement of the thorax a conception which has excited much comment but which has never been established Kountz and Alexander have shown that many of the cases which occur in older people and which have often been called in the literature 'senile emphysema may be dependent upon a *disease of the* intervertebral disks In this condition the spine is at first straightened causing an elevation of the ribs and of the thorax and a displacement of the lungs to a position higher than normal Later, disease of the vertebrae themselves may cause angulation of the spine with kyphosis which still further increases the deformity and abnormal position of the thorax and lungs In some instances pathologic stretching of the lungs may result through this mechanism Although it operates *most often in patients* past middle life it may occur in young individuals with Pott's disease and other kyphotic deformities of the dorsal *spine Recently Kerr has* emphasized this condition as a part of a syndrome which occurs in obese middle aged individuals and which he considered one of the most important seen in the practice of adult medicine In this condition the diaphragm may be pulled downward by the increased weight of the abdominal contents with a consequent mechanical disadvantage in pulmonary ventilation which may simulate to some extent the changes of obstructive emphysema

Changes in the Pulmonary Vessels—The *elasticity* of the lungs *may be impaired by* nutritional disturbances resulting from insufficiency of the pulmonary circulation and particularly from arteriosclerosis of the smaller branches of the pulmonary vessels

Compensatory emphysema results from an overstretching of the airholding portion of the lung when for some reason other parts are not functioning It is always secondary and indicates no essential disease of the distended portions It is seen in uninvolved lobes during pneumonia and occurs with patchy distribution in bronchopneu*monia and tuberculosis* With fibrosis of the lung or with long standing pleurisy it may become permanent

Age—Emphysema due to asthma chronic bronchitis or other partial obstruction may not become striking enough to attract attention for several years after the onset of the primary condition Except in cases from these more obvious obstructive causes the disease is generally seen after middle life *although occasionally it may* develop in young children

Heredity—The possibility of hereditary emphysema has been much discussed Although there are numerous examples of the occurrence of emphysema in several members of the same family many of these may be attributed to hereditary allergy Evidence that individuals are born with weak

elastic tissue and a consequent tendency to early distention of the lungs is not convincing

Morbid Anatomy —The essential pathologic lesion in obstructive emphysema is the loss of elasticity and rupture of the alveoli In the more advanced stages there is fusion of several alveoli into one large air sac Large blebs may be found on the surface of the lung Upon opening the chest the lungs appear to be larger than normal They usually collapse slightly, but may remain distended They are pallid and seem to contain little anthracotic pigment Pallor and distention are often more marked at the apices and at the sternal margins The lungs have a feathery consistency and pit on pressure *Microscopically* the air sacs are greatly distended The epithelium of the alveoli undergoes fatty changes In the bronchi there are evidences of chronic inflammation and there is peribronchial fibrosis Dilatation of the air sacs and smaller bronchi is always noted

The stretching of the alveoli results in changes in the pulmonary capillaries which may disappear before the atrophy of the walls is complete Arteriosclerosis of the pulmonary arteries is not extensive in cases which have resulted from obstructive causes but may be an important feature in a few cases which develop without obvious clinical causes This is usually most notable in the smaller arterioles

The relationship of emphysema to the development of *cor pulmonale* has been much debated Kountz and Alexander have shown that in some patients dying with extreme emphysema the right heart may appear entirely normal More recent observations by these authors and by Scott and Garvin have demonstrated that both in experimental animals and in men strain upon the right side of the heart is an essential part of the disease In advanced cases this may be accompanied by an unexplained hypertrophy of the left ventricle Right heart failure is seen in more advanced form in emphysema associated with disease of the pulmonary arteries

One of the most important functional changes occurring in emphysema is an elevation of the intrapleural pressure which may approach that of the atmosphere

Morbid Physiology —The extensive anatomic changes of hypertrophic emphysema interfere seriously with the exchange of gases in the lungs In advanced stages the oxygen saturation of the arterial blood may be diminished from the normal of about 95 per cent to 90 or 85 per cent or less even during rest During exertion the saturation may be even more greatly diminished There is interference also with the passage of CO_2 from the lungs and a consequent marked increase in the CO_2 tension in both arterial and venous blood

Several factors contribute to this disturbance of function The destruction of air spaces with the diminution of alveolar surface may be of fundamental importance and the degenerative changes in the remaining alveoli may interfere with diffusion of gases It has been suggested by Christie that when the muscles of inspiration are held in an inspiratory position and the lung is inelastic inspiratory effort is ineffective and response in breathing is limited to outlying alveoli many of which are functionless The residual air (the amount of air remaining in the lungs after the deepest possible expiration) is increased so that the air column through which diffusion of gases must take place is greater than normal The vital capacity of the lungs is diminished in the advanced disease to less than half the normal There is some evidence that in emphysema the volume of the dead space is increased The minute volume and the rate of respiration are usually slightly greater the depth of each respiration somewhat less than normal Both the relatively shallow breathing and the increase in dead space render each breath less effective and add to the difficulty All of these factors tend to prevent proper exchange of gases when the patient is at rest while during exercise their effect becomes more evident The oxygen saturation of the arterial blood decreases rapidly and CO_2 accumulates In spite of this the volume of breathing does not increase so much as in normal individuals no doubt because of the diminution in the vital capacity and the mechanical limitations of the emphysematous lung This inability is well demonstrated when an emphysematous patient breathes a 7 per cent mixture of CO_2 and air With this powerful respiratory stimulus a normal individual may increase the vol

ume of breathing six to seven times a patient with advanced emphysema, on the other hand may no more than double the respiratory volume even when higher percentages of CO_2 are employed

One of the more important functional changes occurring in emphysema is an elevation of intrapleural pressure which may approach that of the atmosphere This interferes with the return of blood to the heart and may result in increased venous pressure which is not attributable to heart disease

Symptoms —The onset of emphysema is insidious and the lesions may be well advanced before symptoms become apparent The first evidence is puffiness and shortness of breath on exertion with perhaps moderate cyanosis In winter there may be persistent bronchitis with an increase of dyspnea As times goes on bronchitis becomes more severe breathlessness may result from slight exertion and cyanosis may occasionally become extreme and out of all proportion to the degree of dyspnea or the other symptoms In no condition except congenital heart disease is there such marked cyanosis in ambulatory patients During the course of emphysema attacks of acute bronchitis in association with the advancing emphysema may simulate asthma Throughout the early stages of the disease the patient is much more comfortable in summer but as the process advances there is troublesome bronchitis with chronic cough in both winter and summer Sooner or later symptoms which simulate closely the picture of cardiac decompensation add to the distress of the patient Dyspnea increases orthopnea develops with edema of the extremities In cases complicated by pulmonary sclerosis these symptoms may in part be due to insufficiency of the right heart Ordinarily however the picture probably results from a combination of inefficient lungs anoxemia and increased venous pressure Extraordinary cyanosis may occur in the terminal stage Intercurrent pneumonia is not an infrequent cause of death

Physical Signs —*Obstructive Emphysema* —Chronic emphysema may usually be recognized by inspection The breathing is more rapid and shallow than normal Even in the early stages there may be moderate cyanosis of the lips or lobes of the ears which increases with slight exertion The appearance of the chest is characteristic the marked increase in the anteroposterior diameter gives to the thorax a barrel shape There is an upper dorsal kyphosis The chest is held in permanent inspiration so that the shoulders appear elevated and the neck shortened The intercostal spaces are widened The sternum and intercostal cartilages are prominent The costal angles become obtuse and in extreme degrees of the disease are almost straight There are often small venules along the line of attachment of the diaphragm The apical impulse of the heart cannot be seen but there is usually marked pulsation in the epigastrium During inspiration the chest is elevated as one piece and there is little or no measurable expansion

Upon *palpation* the tactile fremitus is feeble but not lacking The cardiac apex cannot usually be felt To *percussion* there is an increased resonance sometimes almost a tympany The limits of the lung resonance may be extended in some instances to the costal margin The heart dulness may be obliterated and the areas of hepatic and splenic dulness greatly diminished or lost Upon *auscultation* the breath sounds are feeble and are often obscured by the rales of bronchitis Expiration is prolonged and may be four times the length of inspiration Harsh rhonchi may be heard In obstructive emphysema the lungs are so stretched as to force the diaphragm into a position of almost full inspiration Breathing may be entirely thoracic and fluoroscopic examination reveals little motion of the diaphragm with breathing Heart sounds are distant There may be an accentuation of the second pulmonic sound The action of the heart is rarely irregular

Emphysema Dependent on Shape of Thorax —Since in this type of emphysema there is usually less actual stretching of the lungs cyanosis and other signs of functional disturbance are apt to be less marked In the senile cases the thoracic spine is usually straighter than normal the ribs and entire thorax are elevated The breathing tends to be abdominal and in the fluoroscope the diaphragm descends normally or more than normally with inspiration In the advanced cases dorsal kyphosis is a prominent feature

In the syndrome emphasized by Kerr there is great abdominal adiposity which leads to shifting of the line of gravity forward in the erect position The major portion of the dorsal spine is moved backward the thoracic curve is exaggerated, the normal lumbar lordosis becomes more marked and the dorsal and lumbar spines tend to assume the shape of an S

Treatment —Emphysema is a progressive disease the rapidity of its progress depending upon the stress to which the damaged lungs are subjected In the obstructive cases dependent upon asthma the control of the allergic condition offers the chief indication for treatment Particular care must be exercised to prevent the occurrence of bronchitis Whenever possible the patient should live in an equable mild climate during the late fall and winter and should remain until the spring is well advanced Unfortunately such care is rarely possible and to the vast majority of patients who must remain at work during the winter months advice must be given concerning the avoidance of sudden chilling and wetting Clothing should be warm but so adjusted as to prevent perspiration within doors or chilling without Sudden changes in temperature involved in going outdoors from an overheated room on a cold winter day are particularly dangerous The feet should be carefully protected against wet Dusty occupations heavy lifting or severe prolonged exertion should be avoided

Great help has been obtained by many patients with emphysema through the use of an abdominal belt as devised by Alexander and Kountz A newer belt described by Kerr provides flexibility by means of elastic webs inserted in the sides It is effective both in obstructive and postural emphysema and is simpler to construct and easier to wear than the original belt The proper adjustment of such a belt tends to increase intra abdominal pressure causes demonstrable elevation of the diaphragm and more effective breathing Medication does not affect the course of the disease but may provide symptomatic relief Ephedrine in doses of ⅜ to ¾ grain (25–50 mg) may be helpful in relieving bronchial spasm not only in allergic cases but also in those with accompanying bronchitis With the appearance of orthopnea and peripheral edema, digitalis may be tried but is seldom effectual in relieving the symptoms

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DISEASES OF THE PLEURA

PLEURISY

(*Pleuritis*)

Definition.—Pleurisy is an inflammation of the pleural membranes parietal visceral or diaphragmatic This inflammation may heal often with resulting pleural thickening and adhesions or may lead to effusion of serous or serofibrinous fluid or to the formation of pus Three chief clinical types are recognized (1) *acute fibrinous pleurisy* (pleuritis sicca), (2) *pleurisy with effusion* (pleuritis serosa pleuritis serofibrinosa) (3) *empyema* (pleuritis purulenta) As a late result of extensive or recurrent pleurisy widespread adhesions and thickening of the pleura (sometimes with persistent effusion) occur resulting in limitation of respiration displacement of the heart and other organs and pain on effort This condition has been

described as (4) *chronic pleurisy* (pleuritis fibrosa)

Etiology —While pleurisy has been ascribed to exposure to cold, or conceivably may result from lodgment of infectious organisms in the pleura without the production of disease elsewhere in the body, it is usually secondary to disease in other tissues of the body It may arise (*a*) by extension of a disease process in the lung as in pneumonia or tuberculosis in which it frequently is a characteristic part of the symptomatology of the disease pulmonary infarcts or abscesses or malignant disease of the lung may extend to the pleura (*b*) by extension of inflammation from adjacent organs as in pericarditis mediastinitis or subphrenic abscess (*c*) by metastatic blood borne infections as in septicemia (*d*) as a symptom in the course of diseases such as chronic nephritis, gout rheumatism or leukemia In pleurisy following trauma or fracture the mechanism is usually obvious although even here the pleurisy may be infectious the trauma and exposure merely reducing local tissue resistance sufficiently to allow the infection to develop

Bacteriology —In pleurisy occurring in the course of a clearly marked disease such as lobar pneumonia septicemia or advanced tuberculosis the bacteriology is commonly that of the primary disease although secondary bacterial invaders may also be found In those cases in which the pleurisy is an early and predominant feature bacteriologic study may indicate the nature of the underlying disease The sputum the chest fluid, and the blood afford material for study The so called primary serofibrinous pleurisy is usually tuberculous (80 per cent) and is secondary to a pulmonary focus sometimes quite small Microscopic examination of such fluids will demonstrate the tubercle bacillus in about 30 per cent and guinea pig inoculation will determine the presence of tuberculosis in still others Serous effusions may occur in streptococcal pneumococcal or other bacterial infections and in such fluids the organisms may or may not be demonstrable Subsequent aspirations may yield purulent fluids In empyema following lobar pneumonia the pneumococcus is usually found

In epidemics of respiratory infections of the past twenty five years, pleurisy, often purulent has been frequent Streptococci have been most often found as in epidemics of septic sore throat or in the streptococcal pneumonias following measles and influenza The organisms predominating in the empyemas following influenza in army camps during World War I varied according to the kind of organism prevalent in the camp communities In some camps streptococci predominated with few instances of pneumococcal infection In others pneumococcal infection was more frequent In a few a peculiarly virulent staphylococcal pneumonia with occasional empyema was met with At Camp Upton Brooks and Cecil found the incidence of empyema was 36 per cent in the streptococcal pneumonias as compared with 11 per cent in the pneumococcal cases In a study of 137 empyemas in a nonepidemic period Lord found pneumococcus in 39 4 per cent and streptococcus in 20 4 per cent At Camp Custer during the influenza epidemic there were very few pneumococcal pneumonias and most of the empyemas were due to hemolytic streptococci Among other organisms occasionally found in the fluid of empyema are *Streptococcus mucosus capsulatus* Friedlander's bacillus *Staphylococcus aureus* typhoid bacillus diphtheria bacillus and *Bacillus pyocyaneus*

In purulent pleurisy resulting from extension of abdominal infection such as appendicitis or liver abscess, from rupture into the pleura of a lung abscess or from perforation into the pleura of malignant disease of esophagus or stomach organisms such as the colon bacillus and various saprophytes may be found

Morbid Anatomy —The inflammatory changes in the pleura may be unilateral or bilateral sometimes involving only a small circumscribed area or, extending over the entire pleural surface of one side In acute fibrinous pleuritis the membrane loses its luster becomes roughened because of deposition of fibrin, and is more vascular than normal Proliferation and detachment of the endothelial cells of the pleura occur with increase of the subendothelial connective tissue and leukocytic infiltration of the inflamed parts In some instances the fibrin forms a very thin membrane in others a

thick creamy layer Fibrinous pleuritis may leave behind little or no evidence of its presence, or the parietal and visceral pleurae may become bound together by adhesions which in some instances are so dense that they entirely obliterate the pleural cavity These adhesions may produce displacements of the mediastinal structures and heart

In serofibrinous pleurisy in which in addition to the fibrinous exudate there is an exudation of serum from the capillaries the quantity of the effusion may vary from a small amount to as much as 4 or 5 liters The fluid is sometimes encysted by interlobar or parietal adhesions The exudate has a specific gravity of 1 016 or more is rich in albumin often coagulates quickly on standing contains leukocytes red blood corpuscles and endothelial cells and chemically it may contain cholesterin uric acid and sugar In most cases it has a light straw color but it may sometimes be hemorrhagic In empyema the fluid is turbid or purulent and contains large numbers of polymorphonuclear leukocytes and often large flakes of fibrin

When the quantity of effusion is large the lung is much compressed In extreme cases the lung may be reduced to a small flattened airless mass which lies in the posterior and upper part of the chest approximately between the levels of the third and sixth dorsal vertebrae Downward displacement of the diaphragm depresses the liver and the spleen As the result of the increased intrapleural pressure on the affected side the heart is displaced toward the opposite side a change which is more marked in left than in right sided effusions The heart however is displaced as a whole and even in extensive effusions on the left side there is no rotation of its apex The other contents of the mediastinum such as the great vessels and the trachea are also displaced

When suppuration in the pleura (empyema) has occurred the pleura is grayish white or yellowish in color and may be greatly thickened The inflammation may be general or circumscribed with sacculation of the fluid Interlobar encapsulation of the effusion is not uncommon If long continued the inflammation may lead to penetration of the soft tissue of an intercostal space with a resultant external discharge of pus (empyema necessitatis) or the inflammation may extend into the interstitial tissue of the lung Pleural suppuration may also extend to the pericardium or to the mediastinum and be complicated by endocarditis cerebral abscess or thrombosis of the intrathoracic or other vessels While rarely empyema may extend downward through the diaphragm it is much more common for infection in the abdomen such as that of appendicitis to extend upward to the pleura The exudate of pneumococcal empyema contains large flakes of fibrin that of streptococcal empyema very little fibrin In empyema following abscess or gangrene of the lung or perforation of a viscus the fluid may be putrid The specific gravity of empyema fluid varies between 1 024 and 1 030 or even higher and the predominating cell is the polymorphonuclear leukocyte The color of the fluid is usually yellowish sometimes with a greenish tinge The consistency is thin at first and later so thick as to render aspiration difficult

Ernest E Irons

ACUTE FIBRINOUS PLEURISY

Symptoms—Acute fibrinous pleurisy usually has an abrupt onset manifested by a stitch or pain in the side Some types of dry pleurisy usually the more chronic are not painful Acute pleurisy often marks the onset of acute infectious disease such as lobar pneumonia or occurs in the course of a clearly defined infection or is an early event in pulmonary tuberculosis which has hitherto produced no recognizable signs

In other cases the symptoms are limited to those caused by the pleurisy itself Often there are prodromal symptoms such as cough and expectoration In some cases the onset of pain is accompanied by a chill The pain is stabbing or cutting in character is increased by deep respiration is commonly aggravated by coughing or by change of position and is usually located in the fifth or sixth intercostal space in the midaxillary line or beneath the scapula Pain may be felt in the shoulder in apical pleurisy or referred to the neck or abdomen in diaphragmatic pleurisy The location of pain caused by pleural irritation depends on the

location of the pleurisy with reference to the nerve supply of the pleura to our knowledge of which much has been added by the excellent studies of Capps *The visceral pleura* has no pain sense, the parietal pleura secures sensory fibers from the intercostal nerves and pain is felt over the region of the pleura involved The central portion of the diaphragmatic pleura is innervated by the phrenic nerve and pain originating here is referred to the neck and skin and tissue overlying the trapezius muscle, supplied by the third and fourth cervical nerves The peripheral and posterior portions of the diaphragmatic pleura are innervated by the last six thoracic nerves and pain from irritation of these portions of the diaphragmatic pleura is referred to the lower chest wall lumbar region epigastrium, or lower abdomen Such referred pain may render diagnosis difficult by simulating that of certain abdominal diseases such as inflammation of the gallbladder or of the appendix

About 75 per cent of the patients suffer from a cough which is usually dry hacking and suppressed and which aggravates the pain The respiratory rate is usually increased as the result of the patient s effort to lessen the coughing and pain by limiting the excursion of the lung Fever is often present the temperature rising to 102° or 103° F

Physical Signs —The patient shows evidence of distress and lies on the affected side with the shoulder depressed and the upper part of the spine deflected toward that side *in order to reduce the expansion of the lung* The respiratory rate is increased so that the pulse respiration ratio may approach that of pneumonia If there is much fibrinous exudate, the tactile fremitus is decreased and the expansion of the affected side is limited Occasionally there is marked tenderness of the skin over the region of the pleurisy and a *friction rub* is often palpable The percussion note may be unimpaired but if there is much exudation of fibrin its resonance will be decreased

The rubbing together of the roughened surfaces of the pleura produces an audible to and fro leathery *friction rub* synchronous with the respiration except during the early stages of the disease when superficial crepitations—the so called *pleural crackles*—can be heard The most common site of the friction rub is in the midaxillary line in the fifth or sixth interspace When the pleurisy is near the border of the heart the friction sound may be synchronous with the movements of the heart It is then called a *pleuropericardial* friction rub The intensity of the breath sounds is less on the affected side though they still retain their vesicular character

In the majority of cases the leukocyte count varies from 8000 to 12 000 In about 40 per cent of the cases it is above 12 000 sometimes reaching 20 000 When the pleurisy is a complication of pneumonia the figure may be still greater

The *progress of acute fibrinous pleurisy* varies The acute stage with fever lasts about ten days and the entire course of the disease is usually about three weeks When it is more prolonged the pleura often remains considerably thickened Serofibrinous pleuritis may develop with decrease or disappearance of pain

Diagnosis —In most cases the diagnosis of acute fibrinous pleurisy can be made readily from the history of sudden onset of pain in the side which is increased by respiration and coughing and from the presence of friction rub Diaphragmatic pleurisy however, is often difficult to diagnose The conditions to be differentiated from fibrinous pleurisy include pericarditis herpes zoster pain in the side caused by irritation or pressure on nerves in spondylitis or by a mediastinal tumor acute inflammatory conditions of the abdomen and acute myositis

The *pericardial friction rub* is heard best along the left border of the sternum in the third and fourth interspaces is synchronous with the heart movements and is not influenced by respiration The best method therefore for differentiating a pleuropericardial from a pericardial friction rub is to auscultate while the patient inspires as deeply as possible and holds his breath and again while the patient expires as fully as possible and again holds his breath in order to compare the character of the friction rubs in these two phases

The herpetic eruption establishes the diagnosis of *herpes zoster* but before its appearance the pain is often confusing *Neuritis* of intercostal nerves without herpes may be confused with pleurisy and sometimes the

pain of pleurisy in which friction is not demonstrated may be wrongly ascribed to neuritis More rarely the pain of *angina pectoris* is confused with that of pleurisy The relation of pain to effort and the presence of other evidence of cardiovascular disease will aid in determining the cardiac origin of the pain The pains of *tabetic crises* which may involve intercostal nerves are intermittent not related to respiration and other neurologic evidences of tabes dorsalis are usually present The pain from pressure on nerves caused by *spondylitis* or a *mediastinal tumor* is often bilateral and usually of long duration In cases of doubt a roentgenogram of the chest and dorsal spine determines the diagnosis *Loud rhonchi* or sonorous rales can be distinguished from a pleural friction rub by their character and by their disappearance on coughing

In the differentiation of diaphragmatic pleurisy from acute inflammatory conditions in the abdomen such as *acute appendicitis* or *acute cholecystitis* the physician is confronted with a difficult problem If in addition to the taking of a careful history the following points are considered few mistakes will be made During diaphragmatic pleurisy (1) the temperature is higher especially if pneumonia is also present than during abdominal inflammation (2) the pain is increased on deep inspiration and the respiratory rate is increased (3) the leukocyte count is usually higher particularly when there is al o pneumonia (4) other evidences of respiratory infection such as cough cyanosis herpes rusty expectoration and signs of consolidation of the lung may be present (5) pressure over the site of pain relieves the discomfort whereas it increases that of an acute abdominal disturbance (6) nausea and vomiting may be present but less constantly than during abdominal inflammations

Prognosis.—The prognosis of acute fibrinous pleurisy depends on the course of the primary or underlying disease with which it is associated In the so called primary cases in which evidences of underlying disease are minimal or absent the outlook is good A considerable number (30 per cent of Lord s eighty two cases) later develop tuberculosis

Treatment.—A patient with acute fibrinous pleurisy should be given a diet of easily digested foods and should remain in bed for a few days after the temperature has become normal Treatment will be determined largely by the requirements of the associated disease as for example in lobar pneumonia The bowels should move daily Most important is treatment to relieve pain In mild cases the local application of a hot water bottle is sufficient in others relief is secured by the application of a mustard plaster In the more severe cases it is necessary to strap the chest with adhesive tape This should be applied tightly during full expiration and should extend past the middle line both in front and back it should not be allowed to remain in place longer than five days During its removal care should be taken to avoid abrasion of the skin this is most easily accomplished by the use of benzine If strapping does not bring relief of the severe pain a hypodermic injection of morphine should be given It is important in all cases for the physician to keep in mind the possibility of the presence or later development of pulmonary tuberculosis Therefore after the disappearance of the pleurisy the patient should be reexamined at stated intervals and subjected to a routine of rest fresh air extra feeding and suitable occupation

ERNEST E IRONS

PLEURISY WITH EFFUSION

Although it is customary to classify pleurisy with effusion as primary or secondary it is doubtful whether the disturbance is ever primary even if the site of other infection cannot be discovered The majority of cases are tuberculous but any type of infection may attack the pleura by direct extension or by metastatic conveyance of organisms from a distant focus Malignant tumors of the lung and pleura both primary and metastatic may cause pleural effusion

Symptoms—Usually serofibrinous pleurisy sets in abruptly with the signs previously described as manifestations of acute fibrinous pleuritis After a few days the pain decreases as the inflamed pleural surfaces become separated by fluid With the appearance of the effusion there may be dyspnea

which increases as the quantity of fluid in creases If the patient is first seen some time after a moderate effusion has occurred dyspnea may be absent and the presence of fluid may be discovered only on physical examination

In the more severe cases the general symptoms may be pronounced The tem perature seldom rises above 102° or 103° F although occasionally it may reach 104° F Except for moderate morning remissions the fever persists until accumulation of the fluid stops the temperature then falls by lysis Chills followed by sweating occasionally occur Digestive disturbances such an ano rexia nausea and vomiting are sometimes present If the attack is prolonged there may be considerable loss of weight and strength

The dyspnea is at times very distressing especially if the fluid accumulates quickly On the other hand it is sometimes aston ishing to find but little disturbance of breathing when the pleural effusion is large, this can probably be accounted for by the slow accumulation of fluid which permits time for compensation by the opposite lung When the effusion is moderate in amount the pulse rate increases moderately perhaps to 100 per minute

There are cases in which none of these symptoms develop and the only subjective evidence of trouble is that the patient does not feel quite normal

Diagnosis —*Inspection* —The posture of the patient is significant He usually lies on the affected side in order to permit freer expansion of the lung on the healthy side When the quantity of effusion is large he may assume a sitting posture The mobility of the affected side is lessened the degree of immobility depending on the amount of effusion The scapula on the affected side is higher than the other and the spine curves toward the diseased side If the effusion is massive the intercostal spaces may be obliterated and the volume of the diseased side of the chest consequently increased In rare instances there is a slight edema of the chest wall Litten s diaphragm phe nomenon is absent The apex beat of the heart is displaced toward the healthy side and in right sided effusions may be as high as the fourth interspace in the midaxillary line In left sided effusions a pulsation may be seen to the right of the sternum this is not due to the apex beat but to movements of the right ventricle The veins of the neck may be distended

Palpation enables the physician to confirm the results of inspection particularly as to the comparative immobility of the affected side and the position of the apex beat When the effusion is large the trachea may be pushed toward the opposite side The normal outward movement of the costal margin on inspiration is absent on the diseased side Tactile fremitus is diminished or absent over the site of the effusion but on account of the proximity of the compressed lung it may be increased above the upper border of the fluid at a still higher level it may be normal As a result of the thickening of the pleura the tactile fremitus may not be restored until long after the absorption of the fluid but it may on the other hand be retained if the lung is consolidated or if bands of adhesions bind the lung to the chest wall When the effusion is on the right side the lower border of the liver may be displaced downward, when on the left side the spleen may be displaced

Percussion over the fluid reveals an in crease in the sense of resistance to the examining fingers The percussion note is flat and high pitched The upper level of the fluid can be determined more readily by light than by heavy percussion The area of flatness corresponds to the area of absent tactile fremitus and in cases of right sided effusion the area of dulness merges with that of the liver in left sided effusion Traube s semilunar space is obliterated When the effusion is moderate in amount the upper limit of dulness is a curve (*Damoiseau s* curve—Ellis s line) which extends upward and laterally from the spine with its highest point in the posterior axillary line from which it curves downward and forward to ward the sternum In some cases the dulness can be shown to be movable when the position of the patient is changed When the effusion is of moderate amount there is an area of tympany above the level of the fluid —the so called skodaic resonance—which is most easily demonstrated below the clav icle This tympanitic note varies in pitch with opening and closing of the mouth (Williams tracheal tone) during inspiration

and expiration (Friedreich s phenomenon), and when the position of the patient is changed (Gerhardt s phenomenon) Strong percussion occasionally elicits a 'cracked pot" sound With massive effusion the area of flatness may extend to the clavicle In the lower back on the healthy side there is a triangular area of dulness with the base below and the apex slightly above the upper level of the fluid (Grocco s triangle) Various explanations of this phenomenon have been given but the present consensus of opinion is that it is due to displacement of the posterior inferior mediastinum by the fluid When the effusion is moderate in amount a triangular area of relative resonance with the base above and the apex below (Garland s triangle) can be demonstrated on the diseased side in the lower back close to the spine This is due to the presence of the compressed lung near the spine and is most evident after the patient has coughed and breathed deeply

Auscultation at the beginning of effusion into the pleural sac sometimes elicits a friction rub which can be heard near the upper limit of the effusion During the process of absorption the friction rub may reappear as the visceral and parietal layers of the pleura come in contact

In cases of pleurisy with effusion the direct method of auscultation is frequently used in studying the breath and voice sounds A comparison of the breath sounds on the two sides often shows that on the healthy side they are exaggerated by a vicarious emphysema while over the site of the effusion they may be distant or absent according to the thickness of the layer of fluid At times bronchial breathing with bronchophony and rales is heard over an effusion especially in children Bronchial breathing is often heard in the interscapular region over the compressed lung Sometimes as the fluid is accumulating a peculiar high pitched nasal quality may characterize the voice sounds near the upper margin of the effusion (egophony) As a rule however the vocal resonance is much diminished indeed diminished breath and voice sounds are two of the most important physical signs of pleurisy with effusion As the fluid is absorbed the breath sounds become louder and vesicular in character

Auscultation of the heart will frequently indicate a change in its position due to the accumulation of fluid in the pleural cavity This displacement can be recognized by a change in the location of the maximal intensity of the heart sounds Often a systolic murmur can be heard over the displaced heart If the lappet of lung over the left cardiac border is involved a pleuropericardial friction rub may be audible

Roentgenoscopy—Roentgenograms often demonstrate small pleural effusions which are not demonstrable by percussion and are of particular value in locating encapsulated

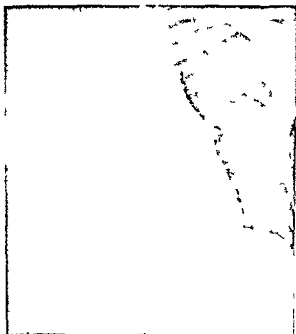


Fig 99—Fluid in right pleural cavity Man thirty four years of age

fluid It is best to expose the films with the patient sitting or standing The fluoroscope offers a ready means of studying the chest in many different positions and reveals the displacements of the heart and mediastinum Roentgenograms taken with the patient lying on the affected side will confirm the presence of small effusions not clearly demonstrable in the upright position

In the majority of cases in which pleural effusion is suspected it is wise to perform an exploratory puncture not only in order to confirm diagnosis but also to obtain the fluid for chemical bacteriologic and cytologic

study The information thus obtained is of value in indicating the primary focus of infection and in determining the type of the invading organism

Diaphragmatic Pleurisy with Effusion—In diaphragmatic pleurisy with effusion the fluid accumulates between the lower borders of the lungs and the diaphragm In general, the symptoms and signs at the onset of the disease are the same as those which accompany the onset of dry diaphragmatic pleurisy In many cases the referred pain in the hypochondrium, the shoulder, or the lumbar region is so marked that there is danger of mistaking the condition for an abdominal lesion

Interlobar Serofibrinous Effusion—The interlobar form of serofibrinous effusion is caused by adhesions which prevent the passage of fluid into the general pleural cavity The characteristic physical signs include some limitation of expansion on the affected side a diminution in tactile fremitus and dulness on percussion over an area which corresponds to an interlobar fissure while above and below this area there may be normal or skodaic resonance The breath sounds are distant over the dull area accompanied perhaps by moist rales As it is often difficult to locate the fluid by exploratory puncture a long needle should be used and the puncture made over the area of dulness keeping in mind the site of the anatomic divisions between the lobes, and avoiding injury to organs and blood vessels Roentgenograms are of great value in detecting interlobar effusions Sometimes an interlobar effusion communicates with a localized effusion in the general pleural cavity thus giving rise to the shirt stud shaped effusion described by Sabourin

Mediastinal Serofibrinous Pleurisy—In mediastinal serofibrinous pleurisy the fluid collects either anteriorly or posteriorly between the mediastinum and the pulmonary pleura The patient often complains of intense pain in the region of the sternum on breathing coughing or swallowing Cyanosis may result from pressure of the effusion on the mediastinal blood vessels Effusions of this type frequently become purulent The area of mediastinal dulness may be widened and a friction rub may be heard to the right of the sternum The diagnosis of this form of pleurisy can best be established by a roentgenogram

Serofibrinous Pleurisy with Polyserositis—When serofibrinous pleurisy is part of a polyserositis there probably will be a pericardial or a peritoneal effusion, or both in addition to the pleural effusion The majority of these cases are tuberculous

Chronic Pleurisy with Effusion—Chronic pleurisy with effusion is comparatively rare and is generally the result of acute effusion which has failed to be absorbed The effusion is frequently pocketed by numerous adhesions Most of the cases are tuberculous With the increase in adhesions' thickening or calcification of the pleura retraction of the chest wall displacement of organs and perhaps the persistence of small pockets of fluid puzzling physical signs may be produced which simulate larger effusions or consolidation of the lung

Differential Diagnosis—With a careful history a painstaking physical examination including a leukocyte count an exploratory puncture and a roentgenogram of the chest the diagnosis of serofibrinous pleuritis can usually be made without much difficulty It is necessary to determine not only the presence of fluid but also its character If the exudate is purulent it is necessary to find the causative organism as the treatment varies according to the type of the invading bacteria for example the treatment of a pneumococcal differs from that of a streptococcal infection

In the differential diagnosis of effusion into the pleural cavity the possibility of one or more of the following conditions must be considered (1) acute lobar pneumonia (2) chronic fibrinous pleuritis, (3) tumors of the lung pleura or mediastinum (4) pericarditis with effusion (5) obstruction or compression of a bronchus (6) pulmonary abscess (7) pathologic conditions below the diaphragm such as abscess of the liver or subdiaphragmatic abscess

Lobar pneumonia is identified by the initial chill high fever rapid respiration and rust colored expectoration as well as by increased tactile fremitus bronchial breathing and bronchophony over the consolidated area Pneumonia does not however always manifest these typical signs Thus if there is a plugging of the bronchus with

mucus or a thick layer of fibrinous exudate over the pleura the tactile fremitus may be absent and the breath sounds distant The *percussion note* over fluid has a flat wooden quality and *offers increased resistance* to the finger It is also difficult to distinguish effusion from pneumonia in cases of high pitched tubular or amphoric breathing Displacement of organs and obliteration of the intercostal spaces are strong evidences of effusion If there is any doubt the physician should make an exploratory puncture with a good sized needle

Chronic fibrinous pleurisy may cause all the signs of a small or moderate effusion but in the former there is no displacement of the heart, or the displacement is toward and not away from the affected side There is little or no elevation of temperature In doubtful cases a fluoroscopic examination of the chest reveals the absence of fluid

Tumors of the lung or pleura may impair the resonance and suppress the breath sounds Absence of fever loss of weight and the discovery of a tumor elsewhere as in the breast or prostate or a history of the previous removal of a tumor often lead to the diagnosis of tumor of the lung or pleura Tumors of the lung can usually be demonstrated by the roentgen ray Tumors of the pleura may be accompanied by an effusion which is frequently bloody and contains a large proportion of endothelial cells As a rule tumors of the mediastinum can be differentiated from mediastinal pleurisy by means of the roentgen ray

It may be difficult to distinguish *pericarditis with effusion* from a left sided pleural effusion The diagnosis of a pericardial effusion is determined by the characteristic shape of the area of cardiac dulness the absence of displacement of the heart intense dyspnea the pericardial friction rub and normal resonance in the axilla between a large area of dulness in front and the area of posterior dulness caused by compression of the lung The latter usually manifests itself in a small area at the angle of the scapula over which the breath sounds are tubular in character

Obstruction of a bronchus by a foreign body or compression by a tumor or aneurysm is evidenced at the base of the lung by the absence of tactile fremitus by impaired resonance and distant or absent breath sounds as well as by the asthmatoid wheeze described by Chevalier Jackson The history the absence of cardiac displacement and a roentgen ray examination of the chest confirm the diagnosis

Patients with subphrenic abscess or other conditions which push up the diaphragm and compress the lungs may manifest signs similar to those of fluid in the pleural cavity Pathologic conditions below the diaphragm do not impair the outward movements of the costal margin from the median line on inspiration The importance of the movements of the costal margin in the differentiation of pathologic conditions below the diaphragm from those above it has been emphasized by Hoover Just as in all other conditions which may obscure the diagnosis of pleurisy with effusion a fluoroscopic examination of the chest and a roentgenogram will aid in establishing the differential diagnosis

Prognosis —The prognosis in serofibrinous pleurisy is fairly good although it is naturally less favorable in patients with active pulmonary tuberculosis Among the 565 cases of pleurisy with effusion collected by Hamman 167 or 29 7 per cent developed pulmonary tuberculosis Unusual sequelae may develop as in the case of a man twenty years old who though showing no signs of active pulmonary tuberculosis developed tuberculous meningitis during the third week of a pleurisy with effusion (Phillips)

Treatment —In the acute stage of serofibrinous pleurisy the patient should be put to bed and given a nutritious and easily digestible diet with extra milk and cream The bowels should move regularly every day If the temperature is high a sponge bath may be given Moderate limitation of fluids and the use of hydragogue cathartics will be of benefit in some cases of pleural effusion but in general the effusion of pleurisy differs from the transudate of passive congestion in that in the former the pleura being inflamed is less permeable and responds less readily to changes in osmotic pressure than does the relatively unchanged pleura in transudates Maintenance of nutrition is more important than efforts to eliminate fluid by limitation of diet and fluids Pleural exudates which have remained sta

tionary in amount for some days are sometimes rapidly absorbed following exploratory puncture Caffeine and theocin may be used for their diuretic action The effectiveness of iodides in promoting absorption has been questioned except in the granulomatous infiltration of syphilis or actinomycosis

Thoracentesis should be performed and the fluid aspirated (1) when the quantity of the effusion is large enough greatly to displace the heart and mediastinum, (2) when the effusion is moderate in amount but has developed so rapidly that the patient is dyspneic and cyanotic and has tachycardia and (3) when the effusion is moderate but fails to be absorbed after two weeks When necessary aspiration should be repeated The site of the puncture should be either in the sixth interspace in the mid axillary line or in the eighth interspace in the scapular line To facilitate the operation the interspaces can be widened by elevation of the arm Some prefer to aspirate the chest with the patient in the recumbent position The *immediate complications* of aspiration may be largely avoided by gentleness the use of sharp instruments adequate local anesthesia and the slow withdrawal of the fluid to an amount not in excess of 1500 cc in an adult

For aspiration a moderate size needle or a small trocar may be used The trocar is less likely to wound the pleura during aspiration but its introduction is often more painful and the outflow of fluid is more likely to be too rapid than when the smaller bore needle is used Negative pressure may be maintained preferably by siphonage by the attachment of a long piece of rubber tubing of small caliber or by the use of a Potain aspirator

The site of puncture is sterilized by application of tincture of iodine or by phenol followed within twenty seconds by alcohol Local anesthesia is obtained by injection of novocain or by ethyl chloride spray which will produce cutaneous anesthesia In introducing the needle the operator should keep close to the upper border of the rib to avoid injuring the intercostal artery Aspiration should be stopped (1) if the patient complains of oppression in the chest (2) if he feels faint, (3) if he complains of severe pain (4) if a paroxysmal cough begins especially when it is accompanied by expectoration of frothy sputum In rare instances sudden death occurs during aspiration probably as the result of a rapid fall in blood pressure produced by irritation of the pleura Capps and Lewis observed that death frequently occurred in dogs subjected to irrigation of the pleura Sudden death has occurred even during an exploratory puncture in some cases the result of air embolism Acute edema of the lungs with albuminous expectoration may develop after the tapping usually when fluid has been removed too rapidly or in too large amount and proves fatal in about 25 per cent of cases This condition is best treated by a hypodermic injection of morphine and atropine sulfate A hypodermic syringe containing this solution should be prepared before beginning the aspiration Occasionally pneumothorax may result from rupture of a vesicle of the lung or from carelessness in technic Subcutaneous emphysema is rare

The best evidence that the fluid is being absorbed and that the patient is recovering is a steady fall in temperature During convalescence all patients should be treated like tuberculous subjects and given rest a nutritious diet and plenty of fresh air If the patient is anemic iron should be given Later he should if possible choose an occupation and climate favorable for the prevention of tuberculous infection

Ernest E Irons

EMPYEMA

(Pleuritis Purulenta)

Etiology —Empyema is seldom if ever a primary infection usually being secondary to an acute pneumonic infection of the lung to pulmonary phthisis to gangrene or abscess of the lung to wounds of the chest wall or to the extension of an infection from the pericardium or abdomen Empyema may also complicate infectious processes in other parts of the body

Symptoms —The symptoms of empyema vary with the disease to which it is secondary In pneumococcal pneumonia the symptoms of pneumonia dominate the picture and the presence of pus may first be

suspected when after an apparent crisis fever and sweats persist, and the patient fails to gain in strength Sometimes the fever and sweating may be slight and the presence of pus may be suspected from physical signs of fluid Persistence of any evidence of in fection such as fever or leukocytosis in a patient convalescent from pneumonia should raise the suspicion of pus in the chest

In the fulminant infections usually strep tococcal which followed influenza measles and septic sore throat during the first World War (1914–1918) pneumonia and acute seropurulent pleural effusions were frequent and are now occasionally met with in local epidemics The symptoms are those of a se vere infection—fever chills tachycardia sweats weakness The temperature ranges from 101° to 103° F and may rise to 104° or 105° F The purulent effusion develops early and rapidly producing dyspnea and cyanosis which may be due in part to coin cident bronchopneumonia There may be an associated purulent mediastinitis

Empyema may follow pulmonary infec tions of less clinical severity and if small in extent and distant from the chest wall may be found only after thorough routine physical examination Suppurative processes in the abdomen especially appendicitis may give rise to empyema the symptoms of which overshadow those of the original cause Cough is often an early and persistent symptom Clubbing of the fingers is occa sionally seen in empyema of long standing There is usually a marked leukocytosis (15 000–50 000) with a relative increase in polymorphonuclear cells Early in empyema following influenza the leukocyte count may be relatively low

Physical Signs —In simple empyema the physical signs are essentially similar to those of pleural effusion The inflammation of lung and pleura incident to pneumonia favors the formation of adhesions which limit the movement of pus and empyema is fre quently found in small pockets so situated as to be difficult of demonstration by per cussion or auscultation One of the most frequent sites is along the interlobar fissure in the right chest In fleshy patients with large chests the physical signs may be ex tremely difficult to demonstrate even when the amount of pus is relatively large Adhe sions between lung and posterior chest wall may further confuse the physical signs in dicative of fluid The empyema suspected by reason of persistent fever and symptoms of sepsis may be just above the diaphragm or in a thin layer along the chest wall or between the lung and mediastinum

Empyema on the left side may pulsate the cardiac impulse being transmitted to the fluid Sometimes there is slight edema of the chest wall over the empyema and fre quently percussion elicits tenderness not found in simple pleural effusion In children the chest wall of the affected side may be more prominent and the interspaces ob literated In cases of long standing the pus may be coughed up or may perforate the chest wall (empyema necessitatis) The latter condition has been mistaken occasion ally for osteomyelitis of a rib

Diagnosis —In pleural effusion the phys ical signs will frequently suffice to indicate the presence of fluid the purulent nature of which is suspected by reason of the signs of persistent infection or sepsis or because of a preceding pneumonia When the history and physical signs are indefinite more dif ficulty is encountered If pus is suspected the exploring needle should be used always with care for asepsis and to avoid injury of organs and tissues The fluoroscope and roentgenogram are of great value and often reveal collections of pus which would other wise be missed It is often desirable to have early and repeated roentgenograms which with the portable machine can be obtained without unduly disturbing the patient On the other hand resort to the roentgen ray as a substitute for careful physical examina tion and study is unfair to the patient and interferes with the acquirement of skill in physical diagnosis

In *subphrenic abscess* the compression of lung by upward displacement of the di aphragm may give physical signs suggestive of empyema Occasionally an abdominal in fection causes both subphrenic abscess and empyema The roentgen ray is of value in making the distinction

Ulcerative endocarditis and *lung abscess* may produce symptoms of fever and sepsis which raise the question of obscure post pneumonic empyema The physical signs of empyema are often erroneously assumed to

be due to *delayed resolution* This mistake may be avoided by the use of the exploring needle and the roentgen ray

In fulminant streptococcal infections of the lung seropurulent effusions may develop rapidly and the dulness and dyspnea are then sometimes wrongly ascribed to extensive pneumonic consolidation rather than to a combination of both In suppurative pericardial effusion the possible persistent pericardial friction rub the outlines of dulness and the roentgenogram will help in distinguishing the condition from empyema

Prognosis—The prognosis in empyema depends on the associated diseases and on the resistance of the individual It is very frequently fatal in children under two years of age (published reports show a mortality varying from 32 to 78 per cent) In children of more than two years the death rate is lower (16 to 26 per cent) For patients of all ages Moschcowitz gives mortality figures which vary from 18 9 to 45 per cent Lord states that of 252 patients in his series 22 2 per cent died in the hospital The use of sulfonamides has reduced the case fatality in children Powers reports twelve cases of streptococcal empyema treated with sulfanilamide and sulfapyridine combined with appropriate surgical procedures with no deaths

The mortality bears a relation not only to age but also to the type of the infection streptococcal infections being more often fatal than those of pneumococcal origin In many cases death should be ascribed to the coexistent pneumonia rather than to the empyema

A neglected empyema may rupture internally into the lung or bronchus or externally through the chest wall More remote results of an untreated empyema may be encountered such as arthritis brain abscess endocarditis and amyloid changes in the liver spleen and kidney

Rare instances have been recorded of perforation of an empyema into other thoracic viscera—trachea esophagus pericardial cavity More remarkable are the perforations of the diaphragm which cause a general peritonitis In even more unusual cases the pus burrows along the spine and psoas muscle to the iliac fossa where it simulates a psoas abscess

Treatment—*The treatment of empyema* varies with the type and virulence of the infection When the quantity of effusion in pneumococcal empyema is small patients occasionally recover completely after aspiration alone Adhesions form early in pneumococcal empyema so that thoracotomy and costectomy can be performed in most cases as soon as the diagnosis is made If however empyema is seen early a *primary aspiration may be advisable* The treatment of pneumococcal and streptococcal pneumonia by sulfonamides has greatly reduced the case fatality but the incidence of complications including empyema has not been correspondingly reduced This may well be due to the survival of the more seriously ill patients who would previously have died Keefer concluded from a study of fifty five cases of streptococcal pneumonia and empyema that the fatality rate in both pneumonia and empyema was reduced by the use of sulfonamide drugs combined with thoracotomy when indicated

In streptococcal empyema adhesions form very slowly Because of this fact and the consequent danger of collapse of the lung because of the danger of infection of the blood stream and because the patient is usually desperately ill, it is wise to aspirate every other day until the pus *becomes thick* and the pneumonia subsides Thoracotomy with resection of a rib should then be performed In these cases it is often difficult to secure adequate drainage as localized pockets are apt to be separated from each other by adhesions These are less likely to develop if aspiration is so frequent *that no* great amount of exudate can accumulate Irrigation of the chest cavity with Dakin s solution has been advocated by some and condemned by others

In old empyema cavities which have persisted in spite of prolonged drainage *resection* of ribs has been employed *allowing* the chest wall to retract with obliteration of the cavity Extensive rib resections have again come into favor in the treatment of tuberculous empyema Each case should be carefully considered before operation is undertaken In cases of pneumococcal as well as streptococcal empyema in *which fever* persists despite adequate drainage as demonstrated by physical and roentgen ray ex

amination search should be made for other sites of infection Coincident ulcerative endocarditis is sometimes found

General measures for the improvement of the strength and nutrition of the patient should be employed in all cases of empyema Fresh air good food and the administration of iron to combat the anemia constitute the chief therapeutic measures Later in convalescence it is important to encourage expansion of the lung by deep breathing or by having the patient blow water from one bottle to another

ERNEST E IRONS

CHRONIC PLEURISY

There are two types of chronic pleurisy (1) chronic pleurisy with effusion and (2) chronic fibrous pleurisy with adhesions (*pleuritis fibrosa*)

Chronic pleurisy with effusion is comparatively rare and is generally considered to be the result of unsuccessful treatment of the acute condition It may be very resistant to treatment because the exudate tends to become pocketed by adhesions Samuel West reports two interesting cases of this type which were finally cured by free incision and drainage In the first the pleural cavity had been aspirated thirty nine times in twelve months in the second the duration of the pleurisy was thirteen months In general however since most cases of chronic pleurisy are of tuberculous origin it is usually wise to avoid incision because of the danger of secondary infection of the tuberculous pleura

Chronic dry pleurisy with adhesions may be a sequel of pleurisy with effusion or may follow an acute fibrinous pleurisy Nearly always even after a mild case of pleurisy the pleura is altered in some degree After pleurisy with effusion there is left between the two pleural surfaces a certain amount of fibrin which undergoes organization with the formation of adhesions between the lung and the ribs or between the lung and the diaphragm These adhesions may be very firm and may even become calcified Subsequent to an empyema that spontaneously drains through the chest wall there may develop very dense adhesions which limit the expansion of the lung or sometimes extensive pulmonary fibrosis with resultant shrinkage of the lung

The only subjective symptoms in these chronic cases are pain after severe exertion and a feeling of limited expansion on the affected side of the chest

Physical Signs—The affected side is smaller than the healthy side and its expansion is limited particularly at the base Litten s diaphragm phenomenon is absent The spine is curved and concave toward the diseased side The shoulder and nipple on the diseased side are lower and the intercostal spaces are narrower than on the healthy side and the outward movement of the costal margin on deep inspiration is limited Tactile fremitus is diminished the percussion note is impaired and the breath sounds are comparatively feeble over the area of pleurisy

An x ray examination of the chest shows thickening of the pleura deformities of the diaphragm and displacement of the heart and mediastinum toward the affected side Calcified areas of the pleura appear as circular or radiating shadows

Treatment—The treatment of chronic pleurisy with adhesions is designed to build up the patient by the usual dietetic and hygienic measures and to improve the breathing capacity by appropriate physical exercises and pulmonary gymnastics If pulmonary tuberculosis is suspected the usual routine for tuberculous patients should be instituted

ERNEST E IRONS

CIRCULATORY DISTURBANCES AFFECTING THE PLEURA

The noninfectious conditions which may cause effusion of fluid in any part of the body may operate within the chest According to the character of the fluid produced—serous fluid blood or chyle—these are classified as *hydrothorax hemothorax* and *chylothorax*

Hydrothorax—*Definition*—The term hydrothorax is used to designate a transudation of serous fluid into the pleural cavities This is most frequently the result of cardiac or renal disease

Etiology—Hydrothorax usually occurs as a manifestation of general anasarca but it may be the result of some local obstruction of the circulation of the blood or lymph produced by the pressure of a tumor or of an enlarged mediastinal or bronchopulmonary gland In some cases hydrothorax may be due to cardiac insufficiency without coexistent general anasarca It may then be bilateral but more frequently it develops only on the right side presumably as the result of pressure on the *vena azygos major* by the dilated right auricle Fetterolf and Landis suggest that cardiac hydrothorax may be due to pressure on the pulmonary veins by the dilated portions of the heart When hydrothorax occurs as a part of the edema of renal disease it is usually bilateral

Symptoms—The only symptom of hydrothorax is dyspnea Fever and pain if present are due to some other cause

Physical Signs—The physical signs of hydrothorax are the same as those of pleural effusion The fluid obtained by puncture shows the general characteristics of a transudate, having a specific gravity below 1 015 and containing very little albumin and few cells It clots slowly and contains only a small amount of fibrin

Treatment—The treatment of hydrothorax consists in aspiration of the fluid if the quantity is sufficient to cause marked dyspnea, and in such general measures as are necessary to relieve the underlying condition

Hemothorax—*Definition*—The term hemothorax signifies an accumulation of blood in the pleural cavity It does not include the accumulations of hemorrhagic fluids which occasionally result from a tuberculous pleurisy malignant disease of the pleura hemorrhagic diathesis or pneumococcus pleuritis

Etiology—Hemothorax is usually due to the rupture of an aneurysm to the erosion of an intercostal vessel by a tumor or necrotic rib or to trauma In the first World War the condition was often produced by gunshot wounds or other injuries of the chest and lungs Effusion following pulmonary infarct while usually serous or only blood stained may be composed largely of blood Hemothorax has been reported following snake bite in India

Symptoms—The symptoms of hemothorax may be divided into two groups (1) those due to the pressure of the rapidly accumulating fluid in the pleural cavity—dyspnea and cough, and (2) those due to anemia from loss of blood—faintness, sweating air hunger, rapid beating of the heart and coldness of the extremities After the first day there is some fever If the lung is wounded there is usually hemoptysis

Physical Signs—The physical signs are those of fluid in the pleural cavity and of secondary anemia Exploratory puncture reveals not only blood but also some serous fluid as the presence of free blood always causes the transudation of a certain amount of serum The coagulability of the blood is below normal probably because some change in the fibrinogen is caused by contact with the endothelium of the pleura During absorption the skin may assume a slight icteric tinge

Complications—Infection of the effused blood is the most serious complication Pneumohemothorax is not uncommon and occasionally develops into pyopneumohemothorax Sometimes the injury may cause pneumonia a pulmonary abscess or gangrene A generalized streptococcus septicemia or septicopyemia may at times result The development of either a localized or a generalized infection is indicated by the usual signs—increasing temperature and pulse rate, chills sweats and such local symptoms as increase of the exudate and persistent cough

Diagnosis—The diagnosis of hemothorax can usually be made from the history and physical signs When signs of an effusion into one pleural cavity develop within a few hours after injury they are usually due to hemothorax An exploratory puncture and a fluoroscopic examination of the chest verify the diagnosis

Prognosis—The prognosis is always serious the mortality varying from 30 to 50 per cent

Treatment—The patient should be kept absolutely at rest External wounds should receive the usual surgical care Immobilization of the involved side with adhesive tape aids in controlling the hemorrhage but aside from this symptomatic treatment is usually employed If there is distress from

pressure a slow aspiration may be performed If the hemorrhage is sufficient to cause alarming symptoms active surgical intervention may be required to stop the bleeding Transfusion of blood may be a life-saving measure when there has been a large loss of blood or in cases of infection If the bloody effusion contains pathogenic organisms free drainage is necessary

Chylothorax — *Definition* — Chylothorax is a term applied to an accumulation of milky fluid in the pleural cavity This may consist of pure chyle or of a chyliform serous effusion containing fat droplets which are not derived from the lymph channels In certain cases the fluid may be milky in appearance without containing fat droplets The milkiness in these cases appears to be due to presence of albuminous bodies the exact nature of which is uncertain Blankenhorn however in his report of seven cases of chylous effusion states that he does not believe that definitely milky fluids have ever been found the turbidity of which was not due to the presence of emulsified fat derived from the chyle

Incidence —Chylothorax is of infrequent occurrence Rotmann in 1896 succeeded in collecting forty nine cases from the literature and comparatively few cases have been reported since that date

Etiology —The presence of *true* chylous fluid in the pleural cavity is due to some injury or obstruction of the thoracic duct by trauma by a new growth in the pleura by enlarged glands or by parasites When the effusion is chyliform the pleural exudate may be due to any of the causes of a serous exudate the chylous appearance being produced by fat droplets which have escaped from the disintegrating endothelial leukocytic or tumor cells

Symptoms and Physical Signs —The symptoms and physical signs are those of a pleural effusion The nature of the fluid can be determined only by puncture In true chylothorax the percentage of fat in the fluid may be as high as 10 per cent and a thick cream forms on the surface of the effusion

Prognosis —The prognosis depends chiefly upon the underlying disease which is usually of a grave nature The danger from the primary cause is increased by the pressure of the pleural exudate Of twenty two patients in Rotmann s series only four recovered Slight lesions of the thoracic duct may heal and the duct remain patent

Treatment.—The only specific treatment of chylothorax consists in repeated aspiration to relieve the symptoms of pressure Strapping the affected side may aid by diminishing the respiratory movements and thus stabilizing the pressure Surgical intervention is rarely of value although Helferich reports recovery in one case after thoracotomy In one case of chylothorax seen by the writer in which there were multiple tumors presumably lymphosarcomata involving the mediastinum and upper abdomen with enlargement of lymph nodes in the neck and groins the fluid as well as the tumors disappeared following roentgen ray treatment Fourteen years later after thirteen years of good health the patient died of carcinoma of the urinary bladder with metastases in the regional lymph nodes and liver The receptaculum chyli and thoracic duct were surrounded and moderately constricted by scar tissue without local evidence of tumor

Ernest E Irons

PNEUMOTHORAX

Definition —Pneumothorax is a condition characterized by the presence of atmospheric air or of gas in the pleural cavity Air is rarely present alone but is generally associated with a serous effusion (hydropneumothorax) or a purulent effusion (pyopneumothorax)

Various terms are employed to describe the manner in which the air or gas enters the pleural cavity Thus when air enters through the chest wall as for example after a pleural tapping the condition is called *external pneumothorax* when gas enters the pleural cavity as the result of a rupture of the lung *internal pneumothorax* is the term employed The condition in which the perforation in the wall of the pleural cavity is patent during both inspiration and expiration is known as *open pneumothorax* that in which the opening is closed during both inspiration and expiration *closed pneumothorax* When the perforation is patent during inspiration but wholly or partially closed

during expiration the condition is called *valvular pneumothorax*

History — Although Hippocrates noted the succussion splash he failed to distinguish between empyema and pneumothorax Hewson (1739–1774) observed the presence of air in the pleural cavity and in 1803 Itard recognized the relation of pneumothorax to tuberculosis In 1819 Laennec gave such a thorough description of the symptoms and physical signs of pneumothorax that little has been added up to the present time Forlanini (1895) suggested the use of artificial pneumothorax in the treatment of tuberculosis and since then there has been increased interest in the subject

Etiology — In considering the probable etiology of spontaneous pneumothorax, regard must be had for preexisting pulmonary disease In patients with preexisting pulmonary tuberculosis the usual cause of pneumothorax is caseous ulceration of the pleura Such cases are usually complicated by serous or purulent effusion

Spontaneous pneumothorax in persons previously in apparently good health is not usually associated with active tuberculosis although in some of these the primary lesion may have been a healed tubercle which gave rise to pleural adhesions Of forty six cases followed for two years or more only one was proved to have active tuberculosis (Amberson) The cause of the pneumothorax in this group is believed to be rupture of emphysematous blebs of the pleura or the tear of adhesions Rupture of a bulla in bullous emphysema and the rupture of the mediastinal tissue into the pleural space in mediastinal emphysema have given rise to spontaneous pneumothorax In several cases of streptothrix infection of the lung in which collapse had occurred bullae which projected out from the pleura were easily visible on the x ray film in the area of pneumothorax (H E Potter) Pneumothorax has been noted as a complication of anthracosilicosis in miners Of 199 cases of uncomplicated anthracosilicosis there were seven cases of pneumothorax (3 5 per cent) while in 307 cases complicated by active tuberculosis there were fourteen cases (4 5 per cent) (Sokoloff and Farrell) Coincident emphysema pleural adhesions and severe cough were believed to be contributing factors

Pneumothorax occurs less frequently as a complication of pulmonary gangrene abscess or infarction or other diseases which cause perforation of the visceral pleura such as tumors or echinococcus disease Extrapulmonary causes are subphrenic abscess and lesions giving rise to suppurative processes or erosions of tissue such as tumors and ulcerations of the esophagus and stomach Pneumothorax results also from perforating wounds of the chest and from thoracentesis

Morbid Physiology — Normally the elastic tension of the lungs produces a negative pressure within the pleural cavity which is greater during inspiration than during expiration In thirty six observations Aron found that the maximum pressure during quiet inspiration was —5 09 mm of mercury and the minimum for quiet expiration —2.54 mm of mercury Because of this negative pressure the admission of air into the pleural cavity on one side causes the lung on that side to retract and the heart and mediastinum to be displaced toward the healthy side where the pleura is still under negative pressure In open pneumothorax the external pressure is equal to the internal pressure and consequently respiration is ineffective In closed pneumothorax the internal pressure is increased particularly as soon as effusion occurs Asphyxia may be caused by either open or closed pneumothorax but more frequently by the former In valvular pneumothorax the air enters the pleural cavity during inspiration but cannot escape during expiration and in consequence the intrapleural tension becomes greatly increased and dangerously interferes with the circulation Lord reports that in one case of valvular pneumothorax the average intrapleural pressure was +7 93 mm of mercury at the height of inspiration and +10 48 mm of mercury during expiration In these cases there is a compensatory emphysema of the healthy lung

Symptoms — The onset of pneumothorax is sudden and without any apparent cause The patient is suddenly seized with a sharp, stabbing tearing *pain* in the side of the chest as if something had suddenly given way The pain is usually felt in the mid axillary region but may be referred to the scapula or beneath the clavicle or may radiate around the chest As a rule it is of short duration Accompanying the pain is a *shortness of breath* which steadily increases The

patient is usually found sitting up in bed in great distress with a pale face bathed in perspiration and with cold extremities The *mental distress* is extreme as the patient feels that he is about to die The dyspnea may be so severe that it is necessary to insert a needle into the side in order to allow the air to escape if the air reaccumulates rapidly it may be necessary to repeat the puncture several times Some patients die in spite of repeated tappings in others the dyspnea gradually becomes less severe and the urgency of the symptoms disappears

The severity of symptoms especially of dyspnea depends as in pleural effusion on the rate of accumulation as well as on the amount of air or of fluid in the chest When the pneumothorax develops slowly dyspnea may be absent while the patient is at rest In one case in a young man the condition was discovered by reason of dyspnea on swimming The left lung was almost entirely collapsed yet he had no dyspnea on walking There was no fever effusion or evidence of tuberculosis and when examined one year later the chest was normal

Physical Signs—On inspection the affected side is seen to be greatly distended the shoulder raised and the intercostal spaces widened The respiratory excursion is very slight with no outward movement of the costal margin on deep inspiration The superficial veins are sometimes dilated and there may be slight general edema of the whole side of the chest The heart is displaced toward *the unaffected side and its* impulse may be seen in the new position The patient usually assumes a sitting or half sitting position In Garde s remarkable case the knee-chest position was assumed

Palpation confirms the results of inspection Tactile fremitus on the affected side if felt at all is indistinct in the majority of cases it is entirely absent In right sided pneumothorax the right lobe of the liver may be displaced downward The larynx and trachea may be shifted toward the healthy side If an effusion has developed a splashing ound may be audible when the patient is shaken (Hippocratic succussion splash) Sometimes this can be heard at quite a distance and often can be voluntarily produced by the patient

The *percussion note* varies with the tension of the gas in the pleural cavity, the position of the retracted lung the presence of adhesions the character of the pneumothorax—whether open or closed—and the amount of fluid in the pleural cavity It may vary in quality from tympany to dulness Usually the note is hyperresonant, and if the pneumothorax is large the hyperresonance may extend beyond the limits of the normal lung Occasionally a cracked pot' sound may be obtained which is caused either by the proximity of a pulmonary cavity to the chest wall or by the communication of a large open fistula with the pleural cavity If fluid or pus is present percussion over the lower portion of the pleural cavity elicits a dull or flat tone and a dull area is demarcated from the resonant area by a horizontal line which is in contrast to the curved upper limit of dulness in pleural effusion without air

In most cases *auscultation* shows the breath sounds to be greatly diminished on the affected side and exaggerated on the healthy side This contrast and the hyperresonant percussion note are usually the first signs that lead to suspicion of pneumothorax If an open fistula exists the breath sounds may be amphoric in character and a gurgling sound (the so-called water whistle murmur) may be produced The whispered and spoken voice sounds are decreased Often at the end of inspiration there is a peculiar metallic tinkle comparable to that produced by striking a glass vessel with *a pin This is thought to be due to the bursting* of bubbles of air which have risen to the surface of the fluid from a submerged fistula or to the falling of drops from the walls of the cavity to the surface of the fluid below The coin sound produced by the tapping of one coin with another on the anterior part of the chest while the examiner listens posteriorly is very characteristic It is a ringing metallic sound quite unlike the normal resonance of the healthy lung

Gas Analysis—In experiments on dogs Emerson found that when air is introduced into the pleural cavity the nitrogen content remains constant but the oxygen content quickly diminishes and there is a rapid accumulation of carbon dioxide If the amount of oxygen remains normal the presence of an open fistula is suggested Air is quite

rapidly absorbed from the normal pleural cavity—in most cases within about a week—but when the pleura is diseased the process may take several weeks

A *roentgen-ray examination* of the chest should be made when pneumothorax is suspected The characteristic roentgenographic signs of pneumothorax are abnormal clearness of the affected side absence of the normal lung markings, retraction of the lung displacement of the heart and mediastinum depression of the diaphragm and the horizontal level of the fluid if present If



Fig 100—Total spontaneous collapse (pneumothorax) of the right lung Man forty years of age (A) Collapsed lobes of lung (B) Bleb inflated with air (C) Fluid level within the bleb Subsequent recovery with complete expansion of the lung The outlines of the bleb still could be seen in the x ray film (Courtesy H E Potter)

the patient is shaken waves in the fluid may be observed A *fluoroscopic examination* may show the so called paradoxic contraction of the diaphragm, the diaphragm moving upward on inspiration and downward on expiration

Diagnosis—The recognition of pneumothorax as a rule presents no great difficulty if the possibility of its existence has occurred to the physician The history of a sudden onset of pain and dyspnea, immobility of the affected side with diminished tactile fremitus hyperresonance decrease of the breath sounds displacement of the heart and mediastinum and the presence of the coin sound all indicate pneumothorax

In the *differential diagnosis* one must consider (1) the presence of a large pulmonary cavity (2) subphrenic pyopneumothorax, (3) diaphragmatic hernia, (4) gaseous distention of the stomach and (5) pleurisy with effusion

Pulmonary cavities are seldom large enough to make difficult their differentiation from pneumothorax An enormous cavity might be mistaken for pneumothorax, for the percussion and auscultatory signs could be the same but the onset of cavitation is not sudden and there is no displacement of the heart or mediastinum A roentgenogram will also demonstrate that the diaphragm is elevated rather than depressed

The differentiation of *subphrenic pyopneumothorax* may be very difficult The history will usually indicate the presence of some abdominal lesion such as perforation of a gastric or duodenal ulcer or of the appendix The liver is depressed and the lower portion of the lung compressed There may be resonance or tympany above the level of the compressed lung and movable dullness below with amphoric or diminished respiratory murmur metallic tinkle coin sound and succussion splash The mobility of the chest is not interfered with so much as in pneumothorax and the costal margin on the affected side may move outward The heart is only slightly displaced Roentgenograms show that the diaphragm is pushed upward and that there is a relatively clear space in the costophrenic angle The pus obtained by puncture often has a fecal odor In many cases jaundice is present

Diaphragmatic hernia provides a history of trauma with attacks of colic nausea and vomiting If a barium meal is given the condition can be readily diagnosed

Gaseous distention of the stomach can be easily determined by the passage of a stomach tube or by x ray examination

In *pleurisy with effusion* even though there may be amphoric breathing the succussion splash metallic tinkle and coin sounds are absent

To differentiate surely between hydro and pyopneumothorax an exploratory puncture is necessary

Prognosis—The course and prognosis of

pneumothorax depend to a large extent on the underlying cause The majority of patients die within the first few days Of West s thirty nine patients ten died within twenty four hours eighteen during the first week and the total mortality for seventy four cases was 70 per cent Death during the first day is due either to circulatory embarrassment or to suffocation from a sudden discharge of the contents of the cavity into the bronchi When death occurs later it may be due to the effusion which follows the pneumothorax In other cases death is caused by the original disease which is often tuberculosis Spontaneous pneumothorax of nontuberculous origin is rarely fatal and complete recovery is frequent In one patient repeated recurrences of pneumothorax were noted Fussell and Riesman report only one death among fifty eight cases

Treatment —Absolute rest should be assured and the cough controlled by the administration of morphine The affected side can be immobilized by strapping and the patient should be instructed to avoid deep breathing and coughing if possible

Patients usually recover from spontaneous valvular pneumothorax if left alone but when the respiration and the circulation are greatly embarrassed aspiration should be performed at once to relieve the intrapleural pressure and repeated as often as necessary When the condition is not so urgent it is well to avoid aspiration as long as possible to allow the fistula to close especially in cases of serous effusion when the aspiration should be delayed for two weeks if possible The same plan may be followed in the treatment of pyopneumothorax unless the symptoms of sepsis are too severe If removal of the exudate is indicated aspiration should be followed by resection of a rib and drainage

ERNEST E IRONS

PARASITIC AND OTHER INVASIONS OF THE PLEURA

Echinococcus disease of the pleura is very rare in this country The right pleural cavity is more frequently affected The symptoms often resemble those produced by a slow growing intrathoracic tumor Dyspnea increases progressively Fever is absent but emaciation is common The physical signs are those due to encysted pleural fluid There may be echinococcus cysts elsewhere in the body The blood shows eosinophilia Urticaria is often present In addition to the complement fixation and precipitation tests a skin test using fluid from echinococcus cysts is of value in diagnosis The *treatment* is surgical

In rare instances the pleura may be invaded by *Actinomyces bovis* and by *streptothrix* which produce very similar clinical and pathologic pictures In *actinomycosis* the pleural infection may be an extension from the neck the esophagus or the abdominal cavity Erosion of the ribs and perforation of the chest wall are common features The diagnosis can be established by the presence of granules with branching gram positive filaments and radially disposed club shaped eosin staining bodies The prognosis is grave *Treatment* consists in a combination of the internal administration of potassium iodide and surgical measures

In *streptothricosis of the pleura* the infection is an extension from the lung Clinically the condition resembles tuberculosis There may be multiple pulmonary abscesses The presence of threadlike branching organisms which to a considerable degree resist decolorization with acid and alcohol establishes the diagnosis

ERNEST E IRONS

TUMORS OF THE PLEURA

Tumors of the pleura may be either benign or malignant Benign tumors are extremely rare although lipoma fibroma osteoma angioma and xanthoma of the pleura have been described The lipomata arise either from the subpleural fatty tissue or from the fatty tissue of the thoracic wall

Primary malignant tumors—carcinoma sarcoma and endothelioma—are of rare occurrence metastases from primary new growths in the breasts lungs stomach esophagus or thymus are much more common

Symptoms and Physical Signs —The symptoms and physical signs of malignant pleural tumors somewhat resemble those of pleurisy with effusion As a rule fever is

absent Loss of weight and strength and emaciation are usually marked and there is a progressive secondary anemia The fluid *obtained by* tapping may be straw colored but is not infrequently bloody and has a specific gravity of less than 1 018 It contains a larger proportion of endothelial cells and fewer lymphocytes than the ordinary transudate The presence in the pleural exudate of rosettes of cells or of cells showing mitosis is thought to be pathognomonic of malignant disease of the pleura

Prognosis—The disease as a rule terminates fatally within six months though in some cases death may not ensue for twelve or eighteen months

Treatment—The treatment is symptomatic Aspiration should be performed if the dyspnea is urgent Morphine should be administered to relieve pain or distress There is some evidence that life may be prolonged by the use of radium or by x ray therapy

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DISEASES OF THE MEDIASTINUM

AFFECTIONS of the mediastinum which should be considered as separate entities distinct from the diseases of certain structures within the mediastinum may be divided into two main groups (1) those involving the connective tissue of the mediastinum including acute and chronic mediastinitis mediastinal abscesses mediastinal hemorrhage and mediastinal emphysema and (2) tumors of the mediastinum

Mediastinitis—*Simple mediastinitis* without suppuration may be associated with pericarditis pleurisy pneumonia or syphilis The subjective symptoms are fever pain beneath the sternum and occasionally cough Physical examination reveals no positive changes Crepitations may be heard along the border of the sternum and the area of mediastinal dulness may be somewhat increased The course of the disease is usually comparatively short but the simple form may become suppurative Enlargement of mediastinal lymph nodes as shown in roentgen films is frequent after acute upper respiratory and pulmonary infections In children especially asthmatic symptoms may result from pressure of the glandular masses on the bronchi

Indurative Mediastinitis—In some cases acute mediastinitis is followed by a great increase in the fibrous tissue—indurative mediastinitis—with adhesions and compression of the great vessels Cyanosis dyspnea and cough are the prominent symptoms The superficial veins are enlarged and the mediastinum broadened as may be shown by x ray and by percussion Often a creaking friction rub may be heard There may be associated adherent pericardium When the thoracic duct is compressed or injured fluid if present in the pleura or peritoneum may be chylous

Suppurative Mediastinitis—Some cases are due to a general infection such as erysipelas and pyemia or mediastinal infections may be an extension from an inflammation of the lung or pleural cavity especially during epidemics of influenza and other respiratory diseases The influenza epidemic of 1917 and 1918 furnished many instances of suppurative mediastinitis frequently associated with empyema

The *chief symptoms* of suppurative mediastinitis are fever which tends to be septic in type sweating local pains and a gradually increasing shortness of breath There may be marked symptoms of pressure As the disease progresses there is anemia and wasting The majority of these cases are fatal though in some instances when the pus makes its way to the surface there is ultimate recovery Should the abscess rupture into the trachea or bronchus a large quantity of pus may be coughed up or death may speedily result from suffocation

Tuberculous Mediastinitis—Tuberculosis may involve any of the groups of mediastinal glands but the tracheal and bronchial glands are those most frequently affected Involvement of the intrathoracic glands usually results from the extension of an infec

tion from the neighboring structures especially from the lung or the pleura and occasionally from bone The tuberculous process may extend directly from the glands of the neck or along the lymphatics through the diaphragm to those in the abdomen This condition sometimes follows an acute infection such as whooping cough It is more common in children than in adults That in children enlargements of the tracheobronchial glands are frequently not tuberculous must however be kept in mind as these glands are always enlarged in acute bronchial infections in children and also in so called glandular fever The glands have a tendency to become caseous then purulent thus being a common origin of chronic abscesses within the mediastinum They may perforate into the aorta or pulmonary artery and cause fatal hemorrhage or they may ulcerate into the trachea or into the thoracic duct and thus sometimes cause acute miliary tuberculosis

Symptoms—The symptoms of tuberculous mediastinitis are fever wasting anemia night sweats loss of appetite more or less disturbance in breathing which sometimes simulates spasmodic asthma and coughing which may be spasmodic and croupy in quality or may occur in paroxysms resembling those of whooping cough If the glands should rupture into the trachea the patient may cough up purulent or caseous material In some chronic cases even calcareous fragments (lung stones) may be expectorated Physical examination discloses marked dullness over the sternum particularly when the anterior mediastinal glands are tuberculous Eustace Smith has described in children a venous hum which is audible at the root of the neck when the head is thrown back This he attributes to pressure of the enlarged glands on the venous trunks Whispered bronchophony below the level of the fourth dorsal vertebra usually more marked on the right side than on the left suggests enlargement of the bronchial glands (D Espine s sign) Since these signs are to a certain extent identical with those produced by a small cavity or by certain pleuritic conditions their significance should be established by roentgenograms of the chest which disclose the presence of enlarged glands

Treatment—The treatment of *simple mediastinitis* consists of rest in bed local applications of heat to the sternum and the administration of codeine or morphine to relieve the cough If the disease passes into the *chronic* or *indurative* stage and is associated with adherence of the pericardium and cardiac dilatation digitalis should be given to support the heart In any case the general treatment should be adapted to the underlying condition Thus if the mediastinitis is syphilitic in origin antisyphilitic treatment with mercury and potassium iodide should be given In tuberculous mediastinitis the usual hygienic measures—rest fresh air and extra nourishment—are indicated In chronic suppurative mediastinitis if the symptoms of pressure are not severe an expectant policy may be justified as the pus may burrow toward the surface If the process is acute prompt surgical measures may be required The search for pus is usually difficult however and even if successful rarely saves the patient s life

Mediastinal Hemorrhage —Mediastinal hemorrhage is most frequently due to perforation of the aorta or one of its branches and is rarely recognized during life Trauma resulting in fracture of the sternum or in injuries of adjacent structures may cause mediastinal hemorrhage

Mediastinal Emphysema —Mediastinal emphysema may occasionally result from inflammations in the mediastinum the air gaining access to the mediastinum through a perforation of the trachea or a bronchus or making its way from the neck beneath the deep cervical fascia In some instances the air may extend through the cellular tissue of the neck or even over the front of the chest and give rise to an extensive subcutaneous emphysema The subcutaneous emphysema seen in influenza in 1917 and 1918 originated in the mediastinum and was believed to have been initiated by the rupture of air vesicles near the hilum of the lung and thence to have extended along the interstitial tissue upward into the cervical fascia

True mediastinal emphysema should be differentiated from the so-called *subfascial* or *false mediastinal emphysema* which sometimes results from artificial pneumothorax

The evidences of mediastinal emphysema

are subcutaneous emphysema in the neck and dyspnea if there is great pressure The *physical signs* are a high tympanitic percussion note over the mediastinum and in some cases obliteration of the heart dulness Auscultation may elicit crepitation and distant heart sounds or the latter may be inaudible The x ray film may show air in the mediastinum Hamman has described a peculiar crunching murmur along the left border of the heart synchronous with the heart beat

Treatment should be directed to the underlying cause of the emphysema

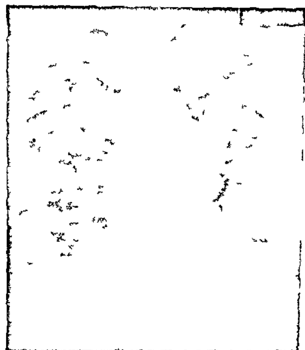


Fig 101—Mediastinal tumor calcified rings Man fifty-eight years of age Slow growth over four years Progressive atelectasis at base of left lung The relatively benign course following x ray therapy and the rounded edges of the tumor suggest that this was not carcinoma but rather a lymphosarcoma or dermoid

Tumors of the Mediastinum—These may be primary or secondary malignant or benign Benign tumors are comparatively rare although fibroma lipoma chondroma myoma intrathoracic adenoma or cyst adenoma of the thyroid simple echinococcus and dermoid cysts have been described

Various forms of *sarcoma* comprise the group of primary tumors which develop most frequently in the mediastinum They are usually primary growths originating in the loose connective tissue of the mediastinum in the peribronchial and mediastinal lymph nodes and in the thymus Secondary sarcoma of the mediastinum may follow sarcoma in the arm leg or other parts of the body while, on the other hand primary mediastinal sarcoma *may be followed by* the development of metastatic nodules in the liver spleen and kidneys

Mediastinal carcinoma is usually secondary to carcinoma elsewhere (for instance in the breast or gastro intestinal tract) but in rare cases is primary

The majority of tumors of the mediastinum develop in patients between thirty and fifty years of age

Symptoms—In considering the symptoms and physical signs caused by mediastinal tumors it is important to have in mind the anatomic structures within the mediastinum which may be compressed These include the superior and inferior vena cava and vena azygos major the aorta and its branches the pulmonary artery, the trachea and bronchi the esophagus, the thoracic duct the heart and pericardium the vagus sympathetic and phrenic nerves the vertebral column and the sternum

The outstanding symptoms are pain or distress disturbance in respiration cough and dysphagia The *pain* which may be constant varies from a feeling of pressure to a burning sensation with periods of acute exacerbation The *respiratory disturbances* vary from a steady progressive shortness of breath to a well defined inspiratory stridor which is often accompanied by wheezing Sometimes, especially in intrathoracic goiter there may be very severe attacks of *suffocation because of the incarceration of the goiter in the superior strait* In one patient *persistent nausea* was relieved by the removal of a large substernal goiter *Cyanosis is often present* When there is profuse pleuritic effusion the patients are *often obliged to maintain the sitting posture* or at times the knee chest position An enormous mediastinal lipoma described by Leopold weighed 17 pounds 6 ounces (7 9 Kg) *The cough* may be paroxysmal but in many cases is the expression *of a constant effort* on the part of the patient to relieve the feeling of obstruction *It frequently* has a curious resounding character—the so called gander" cough The expectoration as a rule is

small in quantity and consists of thin viscid mucus at times however it is profuse mucopurulent or purulent and if the tumor is a dermoid cyst may contain hairs or other characteristic structures The expectoration is often streaked with blood If the tumor invades the trachea there may be profuse hemoptysis

The *dysphagia* is usually due to the pressure of the tumor upon the esophagus, and as the obstruction progresses a pouch like dilatation of the esophagus may form and cause regurgitation of food

In addition to the above symptoms *palpitation* and other cardiac disturbances may be caused by pressure on the heart there may be anginal attacks and inequalities in the radial or the carotid pulse Pressure from the tumor may produce an erosion of the aorta with resultant hemorrhage Venous obstruction may cause an extensive venous thrombosis accompanied by enormous distention of the veins of the upper part of the chest and neck particularly in the rare cases of thrombosis of the superior vena cava The larynx may be fixed so that it no longer ascends and descends with respiration and deglutition The heart may be displaced The aorta and trachea may be surrounded by tumor so that pulsation of the aorta is transmitted to the trachea (tracheal tug)

The principal signs of the presence of a mediastinal tumor elicited by a *physical examination* are a bulging of the chest wall and distention of the veins Sometimes there may be an abnormal pulsation and when the tumor extends above the upper border of the manubrium sterni it can be both seen and palpated There may be cyanosis and swelling of the face neck and upper extremities

In general the physical signs revealed by percussion auscultation or palpation obviously depend upon the position and size of the tumor and the structures to which it is adjacent *Percussion* reveals a widening of the mediastinal area of dulness and if there is obstruction of a bronchus or an accompanying pleural effusion this dulness or flatness may be observed on the affected side of the chest The *auscultatory signs* vary a great deal in different cases When a tumor is situated in the superior mediastinum the quality of the breath sounds may be intensely tubular or amphoric If the trachea is partially obstructed the breath sounds may be feeble throughout both sides of the chest but accompanied by stridor At times a pleuritic friction rub may be heard in the region of the tumor If fluid is present in the pleural cavity the usual signs of pleurisy with effusion are present

Differential Diagnosis.—In the differential diagnosis a careful history and physical examination are of prime importance Of particular significance is the presence of tumors elsewhere or the history of a previous operation for tumor A *fluoroscopic examination* is of value in the final establishment of the diagnosis provided the observations are carefully correlated with the physical findings and the history The mediastinal space should be viewed from different angles and the position of the trachea should be carefully observed as any abnormal variation indicates a displacement of the mediastinal contents

It may be difficult to distinguish a mediastinal abscess from a tumor but when the mediastinal abscess has developed from disease of the vertebrae it usually assumes a fusiform shape gradually tapering off toward the diaphragm In Hodgkin s disease there are often large discrete shadows which correspond to the individual glands and the same is true of leukemia In the latter case blood examination assists in the diagnosis An esophageal diverticulum can usually be readily distinguished from a tumor by means of a fluoroscopic examination after barium has been given by mouth

The differentiation between aneurysm of the aorta and tumor of the mediastinum is of special importance While such time honored signs as expansile pulsation and tracheal tug are suggestive of aneurysm it should be remembered that tumors may rarely pulsate or by their growth about trachea and aorta cause transmission of aortic impulse The fluoroscope and x ray film are of great value in demonstrating the course and size of the aorta

A *laryngoscopic examination* often gives the first clue to the presence of mediastinal pressure by disclosing a paralysis of one of the vocal cords or evidences of compression of the trachea

Laboratory examinations may also be of service For instance when a mediastinal tumor is associated with enlargement of the glands in the supraclavicular space it is often easy to remove one of these glands for histologic examination which may indicate the diagnosis Blood counts are of value particularly in cases of leukemia The examination of the sputum in cases with profuse expectoration or with hemoptysis is of value in differentiating the condition from tuberculosis The finding of teeth and hair in the sputum serves to clinch the diagnosis of the rare dermoid cysts

In general it should be emphasized that the establishment of the diagnosis of a mediastinal tumor should not depend upon any one method but that every diagnostic measure available should be employed the final diagnosis resting upon the correlation of all the findings

Treatment—With the exception of intrathoracic goiters and some dermoid cysts mediastinal tumors can rarely be removed by operation

Fibroid tumors occasionally yield to radiation The growth of carcinomata may be retarded but as tumors of this type are usually metastatic even if the mediastinal tumor is controlled the measure is but palliative and other metastases will almost certainly develop On the other hand the radiation of lymphosarcomata yields quite favorable results these tumors are reduced in size and occasionally permanent benefit is secured

The local involvement of the glands in Hodgkin s disease and in lymphatic leukemia yields readily to radiation but the improvement is temporary

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DISEASES OF THE DIAPHRAGM

THE *diaphragm* bears an important relation to the function of respiration and of circulation It is subject to injuries and diseases just as are structures elsewhere in the body although usually the diaphragm is involved as part of a systemic disease or by extension of disease from neighboring organs and tissues Disturbance of the action of the diaphragm by interference with its nerve supply, or by change in the balance of muscle pull as compared with that of other muscles of respiration results in symptoms of great diagnostic importance Normally because of its arch the diaphragm contracts at a disadvantage and therefore the intercostal muscles gain mastery over it the costal margins moving outward during inspiration When the arch of the diaphragm is depressed however as in emphysema or in pleurisy with effusion it contracts to greater advantage and the costal margins are restricted or move toward the median line The nerve supply of the periphery of the diaphragm is derived from the lower six thoracic nerves and pain caused by irritation of this portion is referred to the lower chest the epigastrium and abdominal wall The central portion of the diaphragm is supplied by the phrenic nerve and pain is referred to the neck and trapezius ridge through the fourth cervical nerve

Inflammation of the Diaphragm—Primary inflammation of the diaphragm is rare but on account of the rich blood and lymphatic supply infection readily extends to it from neighboring organs or a generalized infection may become localized The possibilities of the latter occurrence have been especially studied by MacCallum The muscle of the diaphragm appears to be a favorite site for the lodgment of trichinae a fact which explains the troublesome dyspnea sometimes associated with trichinosis

The pleural covering of the diaphragm is frequently invaded by the agent which causes any generalized or localized pleurisy (diaphragmatic pleurisy)

Symptoms—The chief symptoms of diaphragmatic inflammation are dyspnea a feeling of soreness and a sense of pressure over the lower part of the chest hiccup and pain which is referred to the abdomen

and neck as in diaphragmatic pleurisy The chief physical signs are absence of Litten s sign restriction of motion of the lower part of the chest soreness on pressure suppression of breath sounds at the base of the lung and sometimes the presence of superficial rales along the line of attachment of the diaphragm Fluoroscopic examination of the chest shows decreased mobility of the diaphragm

Prognosis—The prognosis depends on that of the underlying condition

Treatment—The patient should be kept at rest The local application of heat and a binder around the lower part of the chest will relieve the symptoms If the pain is severe it may be relieved by the administration of acetylsalicylic acid codeine or morphine

Spasm of the Diaphragm—Spasms of the diaphragm may be either tonic or clonic in character the latter being much more common and much less serious than the former

The most common form of *clonic spasm* is that known as hiccup Clonic spasms with or without hiccup may be associated with diaphragmatic pleurisy or with any acute inflammatory condition within the abdominal cavity In some cases however the source of irritation is in the central nervous system as in brain tumor apoplexy or encephalitis In many cases the spasms are due to indigestion They are not infrequent in influenza In acute abdominal conditions because of the violent disturbance of the neighboring viscera such spasms of the diaphragm are often of serious import

Tonic spasms of the diaphragm are usually symptomatic of a general condition such as epilepsy tetanus strychnine poisoning or eclampsia they may occur in hydrophobia and in rare instances have been associated with asthma The spasm may be short or prolonged the outstanding symptom dyspnea being intensified accordingly If of long duration and associated with spasm of the intercostal muscles the patient dies of asphyxia

Treatment—*Clonic spasms* of the diaphragm may be relieved by inhalations of ammonia by traction on the tongue or compression of the chest by bromides or in severe cases by morphine Inhalation of carbon dioxide has benefited some cases Hiccup due to indigestion is best relieved by frequent feedings of milk or of milk and cream alternating with the administration of alkalis

Tonic spasms may sometimes be stopped by the application of vigorous counterirritation over the regions of diaphragmatic attachment—the epigastrium the thoracic walls the lumbar region Hot compresses and cupping may prove of value or electric stimulation of the diaphragmatic areas The usual antispasmodics such as chloroform ether and bromides may be employed

Paralysis of the Diaphragm.—The phrenic nerve in its course or at its origin in the cervical cord may be involved in diphtheria in poliomyelitis or in inflammatory conditions of the lungs or pleurae it may be contused by injuries or be pressed upon by tumors or by hemorrhages with resulting paralysis of the diaphragm The paralysis may be unilateral or bilateral the latter being very serious Section of the phrenic nerve is sometimes employed to reduce movements of the lung in pulmonary tuberculosis

Signs and Symptoms—Fowler has described the signs and symptoms of paralysis of the diaphragm as follows (1) reversal of the respiratory movements of the epigastrium and hypochondria with recession rather than bulging in these regions during inspiration (2) absence of the downward movements of the abdominal viscera during inspiration (3) increased outward movement of the lower ribs during inspiration (4) dyspnea on exertion or excitement (5) alteration in the voice and cough (6) loss of the compressive action of the abdominal muscles on the viscera during defecation (7) feebleness of expiration and of such reflex expiratory acts as coughing and sneezing (8) diminution of the total capacity of the thorax as the result of increased arching of the diaphragm The last condition as well as the partial or complete immobility of the diaphragm can be demonstrated by fluoroscopic examination

Prognosis—The prognosis is grave varying directly with the extent of the paralysis When the paralysis is complete fatal asphyxia may follow even the slightest exertion

Treatment should be directed toward improving the condition to which the paralysis is primarily due In some cases the local application of electricity may be of value

Diaphragmatic Hernia —The term diaphragmatic hernia indicates the escape of any abdominal organ through the diaphragm into the chest cavity Three types are distinguished (1) *congenital* due to arrest of fetal development which leaves a defect *in the diaphragm so that organs or tissues* normally placed in the abdomen enter the chest This condition is usually met with in infants many of whom die within a few days after birth In some cases if the condition is not incompatible with life and growth the subjects survive to adult life The order of frequency of such displacements of organs according to Hart is stomach omentum colon small intestine liver duodenum pancreas cecum kidney (2) *Traumatic* the result of stab wounds, blows or in rare instances excessive abdominal pressure as in severe vomiting (3) *Periesophageal* or *hiatus* hernia in which a portion of the stomach passes upward through the esophageal hiatus of the diaphragm Most of these hernias are discovered in adult life and while they may be acquired or may increase in size they probably depend on congenital or abnormal weakness in the periesophageal fascia Formerly believed to be rare they are now not infrequently discovered (60 cases in 8000 examinations Ritvo) during routine fluoroscopies of the stomach For their detection fluoroscopy in the recumbent position preferably with the head slightly lower than the hips is necessary In the routine fluoroscopy of the stomach of 13 034 patients at the Presbyterian Hospital in Chicago there were found 291 diaphragmatic hernias (F H Squire) Very few of these hernias caused symptoms recognized prior to *fluoroscopy as due to diaphragmatic hernia* some were sent for fluoroscopic confirmation of the diagnosis of probable diaphragmatic hernia in the majority the hernia was an incidental finding in patients suffering from other lesions or in normal health and produced no symptoms recognized as referable to it The hernial protrusion varies in size from a small projection perhaps 1 cm in diameter to large hernias *consisting of a* considerable portion of the stomach

Symptoms —The prominent symptoms of *congenital diaphragmatic hernia* are dyspnea and cyanosis The heart is often displaced and a gurgling of gas can be heard in the chest The usual tympany in the left hypochondrium may be absent Distention by gas in the herniated stomach or colon may cause sudden increase in dyspnea or cardiac embarrassment Strangulation of the incarcerated bowel may occur In some cases extensive displacement of stomach or bowel produces slight or no symptoms and the condition is discovered only in routine physical or roentgen examination The majority of infants with this condition die when only a few days old

The *initial symptoms of traumatic hernia of the diaphragm* are those of shock severe pain in the lower part of the chest and a feeling of constriction Hiccup and often dyspnea and vomiting are present *If the* condition is due to a stab wound pleurisy or peritonitis may result The movements of the affected side are limited the heart is displaced a tympanitic note due to presence of stomach or intestine in the pleural cavity may be heard over the base of the lung and gurgling sounds due to movements of flatus heard in the chest

The symptoms of *periesophageal hernia hiatus hernia* (esophageal orifice hernia) are of importance because they *simulate those* of other diseases of the esophagus stomach biliary tract or heart Some are symptomless (14 of 60 Ritvo) The common symptoms are epigastric distress heart burn hiccup eructations of gas and food *especially* on lying down after a meal Dysphagia coming on after two or three *swallows of* food sometimes suggests malignant disease of the lower esophagus Pain over the left trapezius ridge was noted in one case Pain *on swallowing* or at night upon lying down after a full meal may be *severe* and the possibility of cholelithiasis or ulcer is suggested Persistent vomiting *sometimes of blood may occur and* severe anemia has been seen (Weitzen) Bleeding is believed to result from erosions *of the fold* of the incarcerated portion of the stomach Diagnosis depends mainly upon *the fluoroscopic* examination but as more cases *are recog*

nized and the symptomatology studied, the condition in some cases may be suspected from the symptoms Periesophageal hernia must be distinguished roentgenologically from eventration hour glass stomach esophageal or gastric diverticula relaxation of the cardia cardiospasm carcinoma of the esophagus and cardia and symptomatically from conditions such as angina ulcer of the stomach and cholelithiasis

Treatment of the extensive and of the traumatic cases is usually surgical and must be determined after a careful study of each case In many congenital cases in infants satisfactory repair is out of the question



Fig 102 —Diaphragmatic hernia Woman forty two years of age Epigastric pain with vomiting on lying down only

E M Miller (1939) has summarized the literature and added an additional case of successful operation in an infant Frank and Hamilton (1941) report the successful repair of a hernia of the diaphragm in which there was a penetrating ulcer of the herniated stomach The maintenance of the semi erect position has been advocated The danger of strangulation of herniated bowel leads to serious consideration of surgical measures in some cases in which discomfort is minimal Many periesophageal hernias especially the small ones require no treatment They are either symptomless or the symptoms are disregarded by the patient after he has been assured of the cause and more serious conditions such as cancer or ulcer have been excluded Patients with neurotic tendencies may develop aerophagia and various neuroses on the basis of the indefinite or unexplained symptoms The eating of small meals moderate exercise the avoidance of the recumbent position immediately after eating and a diet suitable for ulcer of the stomach diminish symptoms

Eventration of the Diaphragm —The term 'eventration of the diaphragm indicates a defect which is characterized by a thinning or relaxation of one leaf of the diaphragm which occupies an abnormally

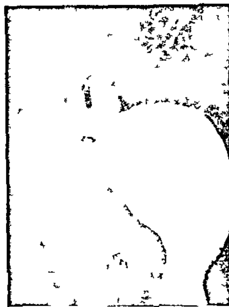


Fig 103 —Diaphragmatic hernia. Woman thirty nine years of age Mild epigastric distress only

high position It is associated in some instances with aplasia of the lung on the affected side The weight of evidence is that it is congenital in origin This condition was first described by Petit in 1790 It is of rare occurrence but during recent years a number of cases have been described

Symptoms—The symptoms of eventration of the diaphragm are indefinite Some patients complain of a rather vague gastric distress The condition is usually detected by x ray examination Funk has called attention to an increased outward movement of the costal margin on the affected side in inspiration which is due to the fact that the intercostal muscles on that side have little

opposition from the weakened diaphragm This observation has been confirmed by Korns

Treatment—Surgical treatment may be of value in certain cases

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ANOMALIES OF URINARY SECRETION

Anuria.—Anuria is total suppression of urine by the kidneys. A satisfactory working classification of the various etiologic causes of anuria divides them into three groups: (1) prerenal, (2) renal, and (3) postrenal. Prerenal anuria is seen in states of shock with low blood pressure where the pulse pressure falls to such a low level that urinary secretion ceases. Anuria of renal origin may occur in (1) the extreme congestion of acute nephritis, (2) from cortical infarction, usually bilateral and occurring postoperatively, (3) following transfusion with incompatible blood which blocks the tubular systems with precipitated hemoglobin, (4) blockage of the tubular system with crystals of the sulfonamide drugs, and (5) in extreme cases of degenerative nephritis caused by such heavy metals as lead, mercury, and phosphorus. A calculus in the pelvis of the kidney may also cause anuria, either unilateral or bilateral, depending upon its location. Postrenal anuria includes those conditions where (1) the ureter is blocked by a stone or new growth, and (2) blockage of the ureter, either unilateral or bilateral, by crystals of the sulfonamide drugs precipitated from the urine. Anuria may follow severe crushing injuries, and rarely the mere passing of a catheter has been known to bring on anuria through reflex nervous action.

In anuria the hydronephrosis which so frequently accompanies partial obstruction of the urinary tract does not tend to develop, and there may be remarkably few *symptoms*. Headache, vomiting, and lumbar pain are the most common. Although nonprotein nitrogen, urea, uric acid, and creatinine are retained in the blood, frequently in even larger amounts than during the terminal stages of uremia, convulsions occur rarely and consciousness is retained almost until death. The reason for this absence of convulsions and constitutional symptoms so characteristic of uremia is not known, but it must be remembered that the mere retention in the blood of any of the recognized nonprotein nitrogen bodies is not in itself sufficient cause for uremia.

Anuria must be clearly differentiated from the condition in which urine is secreted by the kidneys and retained within the bladder. This distinction can be made by either physical examination or by catheterization. Stricture of the urethra, prostatic obstruction, or a spinal cord lesion interfering with the nervous control of the bladder may cause retention of urine. Bladder tumors are suprapubic and median in location.

The severity of anuria varies directly with the duration, which may be several hours or many days. Adams has reported recovery after total suppression of urine for nineteen days.

Treatment.—Treatment of the anuria associated with shock is dependent upon the shock therapy, which is designed to restore the plasma protein and blood volume, elevation of the blood pressure and restoration of the pulse pressure. In the treatment of anuria associated with acute nephritis, hot applications, free purgation, and high hot colonic irrigations have proved valuable. Intravenous administrations of glucose (300 cc. of a 20 per cent solution twice a day) are also beneficial. Intravenous administration of hypertonic (150 cc. of 10 per cent) sodium chloride solution has been reported to be effective. Similar therapeutic measures are advisable when anuria is due to the extreme degeneration caused by chemical poisons. Anuria following transfusion with incompatible blood may be severe and protracted. Recovery occurs in about 80 per cent of the cases with no residual damage of the kidneys. Complete blockage of a ureter with crystals of the sulfonamide drugs demands intravenous administration of large quantities of saline and may require surgical drainage of the pelvis of the kidney and lavage of the ureter. In cases caused by stone in the ureter or by obstruction of the ureter through new growths surgical treatment is imperative.

Hematuria—Hematuria is the discharge of blood in the urine In a small percentage of cases the source of the hemorrhage can not be located but in the majority, various available signs permit determination of the correct etiology

Essential hematuria is the term applied to hematuria of unknown origin and comprises 2 per cent of the total cases In this bleeding is usually spontaneous painless intermittent and not so severe as to lead to exsanguination Certain cases included in this group have been caused by varicosity of the veins of the kidney pelvis or papillae Ureteral catheterization has demonstrated that the hemorrhage of essential hematuria is usually unilateral X ray examination is always negative This condition is usually found in individuals less than thirty years of age

Hematuria of Known Etiology—In by far the larger number of cases hemorrhage can be located and ascribed to a definite cause

1 Renal Disturbances—Acute nephritis pyelonephritis and the acute exacerbations of chronic nephritis especially when the kidneys are secondarily contracted may be accompanied by hematuria of all degrees of severity Passive congestion of the kidneys during marked cardiac failure is a common cause for the presence of a few red blood cells in the urine New growths especially hypernephromata cause profuse bleeding In both early and advanced tuberculosis red cells as well as pus corpuscles appear in the urine but without pyogenic organisms unless there has been secondary infection Other causes of renal hematuria are certain chemical agents such as urotropin turpentine cantharides and carbolic acid the renal infarction secondary to endocarditis and such systemic diseases as purpura, leukemia and malaria The sulfonamide drugs may cause hematuria and rarely it has followed from the use of heparin to prevent the formation of a thrombus Stone in the kidney is the commonest cause of renal hematuria

2 Pathologic Conditions of the Urinary Tract and Bladder—Among the most frequent causes of hematuria are stone in the ureter or bladder tumors of the bladder or prostate tuberculosis ulceration and rupture of the veins of the bladder Occasionally gonorrhea may cause bleeding from the urethra

3 Mechanical Disturbances—Traumatic rupture of the kidney bladder, or posterior urethra as well as injury of the urethral mucosa by catheterization, may also produce hematuria

4 Other Causes—Strenuous exhausting physical exercise and exposure to cold are frequently followed by the temporary appearance of a few red blood cells in the urine without evidence of renal disorder Hematuria has occurred after the use of tetanus antitoxin an allergic manifestation When the blood prothrombin is low due to a deficiency of vitamin K mild degrees of hematuria are seen

Diagnosis—In all types of hematuria red blood cells frequently crenated and albumin are present in the urine As blood cells disintegrate rapidly in alkaline urine the specimens should be examined promptly after collection

The exact character of the *urine* depends on the source of blood There are several means by which this may be ascertained If blood appears at the beginning of micturition it comes from the anterior urethra, if at the end from the vault of the bladder as a rule and if throughout micturition it is mixed with the urine hemorrhage is from the kidney In the latter case blood clots and blood casts may be present and the color of the urine varies from a smoky tinge to bright red Not infrequently children and young adults void bright red urine which is referable to the pigment of beets

Frequently however special examination is necessary before the point of bleeding can be exactly located Cystoscopy ureteral catheterization and intravenous excretory urograms are of great value

Hemorrhoids as well as vaginal discharges may be confusing factors A diagnosis of *essential hematuria* can be made by a process of elimination and should be accepted with reluctance In essential hematuria be suspicious of an early malignancy

Treatment—Rest in bed supplemented by full doses of morphine if necessary is indicated in hematuria of whatever type Cold applications to the lumbar region are often helpful In certain cases of essential hemat

uria recovery has followed simple distention of the pelvis of the kidney with fluid while in others intrapelvic lavage with silver nitrate and adrenalin has proved of only temporary benefit Moccasin venom which seems to exert some action on the capillaries has been successfully used in essential hematuria Also the intravenous injection of the sodium salt of cevitamic acid has stopped the hematuria in obscure cases which would argue that there is a lack of an intercellular cement substance which the vitamin C supplies When hematuria is related to deficient blood prothrombin vitamin K administration will correct it Vitamin P the capillary permeability vitamin when used in conjunction with vitamin C has been successful in controlling hematuria in several diseases Nephrectomy should be performed only as an emergency measure in the most severe cases of unilateral bleeding

Hemoglobinuria —Hemoglobinuria occurs when the blood destroying organs are unable to handle all the damaged red blood cells in circulation and hemolysis consequently takes place in the blood stream Normally the endothelial cells of the spleen bone marrow and hemolymph glands take up these damaged corpuscles and convert their iron containing pigment in part into bilirubin which is carried by the circulation to the liver for excretion Under these conditions the iron forming fraction of the molecule is separated by hepatic action and retained for further use in the body while the remaining portion is converted into bile pigment and excreted Hemoglobin has a renal threshold in man but in terms of its plasma concentration this threshold is very variable It is most constant in terms of hemoglobin per kilogram of body weight 92 mg per kilogram for men and 72 mg per kilogram for women The threshold mechanism operates in the kidney similar to that of glucose excretion namely mechanical filtration through the glomeruli followed by reabsorption by the tubular epithelium Only when the concentration in the glomerular fluid exceeds the absorptive capacity does hemoglobin pass into the urine

Hemoglobinuria falls into two groups (1) toxic and (2) paroxysmal

Etiology —The etiology of the toxic form is variable Chemical poisons such as carbolic acid potassium chlorate pyrogallic acid carbon monoxide muscarine and cobra venom may produce rapid hemolysis while the toxins generated by the exciting agents of certain infectious diseases not infrequently have a similar result Those of scarlet fever yellow fever, typhoid syphilis and certain types of hemolytic jaundice should be cited In malaria hemolysis is caused by the plasmodium which actually enters the red corpuscle multiplies and finally causes rupture Sometimes hemolysis follows the introduction of foreign protein into the blood stream as for instance in transfusion and serum therapy or after extensive burns when the tissue proteins are partially split Rarely hemoglobinuria may be due to a lesion of the kidneys such as infarction and usually occurs only on the side involved Finally exposure to cold and violent exercise are said to increase the fragility of the red cells so markedly that their hemoglobin is liberated and hemoglobinuria ensues This has been noted in young soldiers following strenuous exertion It is interesting that in two conditions namely acute nephritis and infarction of the kidney hemoglobinuria may occur without hemoglobinemia

When hemoglobin is present the color of the urine varies from red to dark brown If specimens are allowed to stand a heavy brownish sediment precipitates Microscopic examination of the sediment reveals no formed red cells but the spectroscope demonstrates the characteristic bands of hemoglobin Causes other than hemoglobinuria that may cause pink red or black urine are hematuria porphyria (urofuscin) myoglobinuria pigment of beets phenolphthalein and neoprontosil

Treatment —The form of treatment depends upon the etiology

Albuminuria —The term albuminuria as employed clinically means proteinuria and is evidence of increased permeability of the glomerulus and Bowman s capsule to large protein molecules Etiologically there are two types physiologic and pathologic

Physiologic Albuminuria —ORTHOSTATIC ALBUMINURIA —For the type of albuminuria in which serum protein mostly albumin appears in the urine only after standing or sitting and disappears after reclining the term orthostatic albuminuria is employed

This type which is most commonly seen in young patients seems to occur usually in thin individuals with poor muscular tone and marked evidence of vasomotor instability

There are two main theories as to its *etiology* (1) that of Erlanger and Hooker which ascribes the albuminuria to diminished pulse pressure and (2) that of Jehle which is based on the belief that the increased lordosis frequently present interferes *with the renal circulation Later studies by* Rytaud following diodrast injections have shown anatomic renal defects which may be a causative factor

Careful studies of renal function have also shown some impairment although of a transitory nature which occurs synchronously with the albuminuria

The quantity of albumin in the urine varies from a faint trace to as much as 8 to 10 Gm per liter Casts are rarely present

It is interesting to note that during orthostatic albuminuria when the body is horizontal a low pulse pressure artificially produced by mechanical lordosis causes albumin to appear in the urine

In many patients the condition is outgrown or disappears as the general state of health improves in others correction of lordosis with a spinal brace is beneficial The prognosis is good

Pathologic Albuminuria —1 Secondary to Nutritional Changes —Normally the kidneys do not permit transmission of serum albumin through the glomerular epithelium into the tubules but circulatory changes may so alter the permeability of the membrane that the protein can pass As soon as renal circulation *is reestablished* however excretion of albumin stops Albuminuria of this type occurs during passive congestion of the kidney severe anemia and after strenuous muscular work and cold bathing The quantity of albumin eliminated in the urine is usually small If casts are present they *are of the hyaline or granular type*

2 Secondary to Toxic Action —Slight albuminuria accompanies the pyrexia of all the acute infections The cloudy swelling of the tubules which is caused by the toxemia rapidly disappears during convalescence In this type the urine may contain a *few* casts

Chemical poisons also produce varying grades of albuminuria by their action upon the kidney Mercury lead ether and chloroform are the more common of these *Exposure to intense sunlight* is frequently followed by a transitory albuminuria

3 Associated with Definite Lesions of the Genito urinary Tract —(*a*) In such organic diseases of the kidney as acute subacute or chronic nephritis the degree of albuminuria varies greatly and is dependent upon the nature and severity of the injury of the glomerular capillaries During advanced chronic interstitial nephritis with primarily contracted kidneys only the faintest trace of albumin may be excreted while during nephritis of the chronic parenchymatous types when the contraction is secondary very large amounts are present in the urine Albuminuria occurs as well in suppurative nephritis amyloid or fatty degeneration of the kidney and as the result of many new growths in the kidney

(*b*) It also follows infection of the renal pelvis ureter bladder prostate and urethra With pus or blood in the urine there *is al*ways a small amount of albumin but usually there are no casts

Prognosis —Within recent years our interpretation of a small quantity of albumin in the urine has undergone a change In young patients albuminuria cannot be considered pathologic until the possibility *of cyclic or* orthostatic albuminuria has been excluded A trace of albumin in the urine after the fortieth year may be merely an evidence of the retrogressive changes of age and frequently goes hand in hand with the slight rise in blood pressure which is physiologic *If associated with increased* arterial tension or the presence of casts or red blood cells in the urine albuminuria is of significance but cannot be truly evaluated without careful consideration of the past *history and* physical condition of the patient

Albumosuria —When proteoses enter the blood stream the tissues seem to be unable to use them and they appear in the urine This is known as albumosuria or proteosuria It is a condition associated with the rapid breaking *down of tissue* such as occurs in suppuration of all kinds intestinal obstruction severe burns resolution of pneumonia involution of the uterus acute yellow at

rophy and leukemia In chronic degenerative parenchymatous forms of nephritis both albumin and globulin are excreted in considerable quantities

Myelopathic Albumosuria —This term is used to denote the presence in the urine of a protein first described in 1818 by Bence-Jones as a new substance This is not a true albumose but is allied to the more simple proteins It seems to be definitely related to diseases of the bone and appears in the urine of about 80 per cent of the cases of myeloma In leukemia, chloroma myxedema (one case reported by Fitz) and nephritis it has also been found in the urine

The quantity recovered in the urine bears no relation to diet The output is constant throughout the twenty four hours and in some cases of myeloma amounts to 30 to 70 Gm daily Just how the kidney can excrete such quantities without organic change or simultaneous filtration of serum albumin is difficult to explain

The exact source of this Bence-Jones protein is not known but the fact that the body cells react to its presence by the formation of a 'precipitin proves it to be synthetic It coagulates at temperatures between 49 and 60 C does not dialyze is precipitated from urine containing 25 per cent nitric acid in such a form that it disappears on boiling but reappears on cooling and gives up sulfur in the presence of alkalis

Treatment depends upon the etiologic basis of the condition Multiple myelomata run a fatal course Benzol has been advocated as a therapeutic measure for this type of albumosuria in leukemia

Bacteriuria.—It is well known that a few bacteria frequently filter through the kidney epithelium and are passed in the urine without causing any symptoms or cellular reaction When large numbers appear in the urine the condition is termed bacteriuria or bacilluria This is of two types—primary and secondary The primary which is the more common is associated with cellular reaction and is caused by a focus of infection in the genito urinary tract The urine is characteristically cloudy when voided and contains pus cells When the cause of the condition is tuberculous pyogenic organisms are usually absent More recent studies have indicated that in primary bacilluria there is usually a local lesion in the cortical area of the kidney Secondary bacilluria is not uncommon in the acute infections in which there is a general systemic distribution of the organisms as frequently found in staphylococcic and streptococcic septicemias It accompanies typhoid fever, pneumonia in many cases and the early stages of meningococcic meningitis Recent observations tend to indicate that in many secondary bacillurias there are local lesions in the cortex of the kidneys

Treatment —In the treatment of primary bacteriuria the sulfonamide drugs hold first place For the coccal infections one should use sulfathiazole in doses of 2 to 4 Gm (30 to 60 grains) per day Sulfanilamide in similar dosage is most effective in colon bacillus infections

Pyuria —Pyuria is the presence of pus in the urine It is a condition associated with infection of any part of the genito urinary tract from Bowman s capsule in the kidney to the external meatus of the urethra

The *causes* fall naturally into three groups (1) pyelitis pyelonephritis and pyonephrosis (2) cystitis (3) urethritis of gonorrheal or other origin and tuberculosis or rupture of abscesses of the genito urinary tract

The presence of significant quantities of pus in the urine is evidenced quite definitely by cloudiness at the time of voiding by the precipitation on standing of a stringy grayish precipitate which can be differentiated from the phosphates with heat and acid and from the urates by heat alone and by the presence of albumin Microscopic examination is of course the surest test Normal urine contains only a few well preserved leukocytes

In determining the exact cause of pyuria several facts must be kept in mind During pyelitis and the pelvic inflammation produced by a calculus pyuria is usually constant That resulting from tuberculosis of the genito urinary tract is also persistent During pyonephrosis and the conditions associated with large abscesses of the kidney on the other hand pus may be discharged intermittently into the urine The chemical reaction of the urine in pyuria caused by cystitis varies according to the type of infecting organism and in tuberculosis of the

genito urinary tract is acid Pyuria of tuberculous origin is not accompanied by bacteriuria Large quantities of pus may be present after rupture of an abscess into the genito urinary tract Certain confusing factors must always be considered before diagnosis is made definite Differentiation between cystitis and chronic prostatitis or abscess of the prostate is necessary In the female the absence of leukorrhea should be ascertained by inspection and catheterization In all chronic cases of pyuria which are resistant to treatment one should be careful to rule out tuberculosis

Treatment—The sulfonamide drugs are most useful in treatment Make a smear from the urinary sediment and stain by Gram s method Then use the appropriate drug according to the type of organism present sulfathiazole for coccal infections and sulfanilamide for gram negative bacillus infections No known drugs are effective with B proteus infections

Chyluria, Nonparasitic—Chyluria and lipuria of nonparasitic origin are essentially the same In both there is fat in the urine The only point of difference is that in chyluria none of the fat is visible as minute droplets while in lipuria most of the fat is in a fine suspension

Fat is present in the urine more commonly than was formerly supposed Although small amounts are frequently found in the urine of patients with *diabetes mellitus* when it is accompanied by lipemia and in nephritis especially of the parenchymatous type as much as 6 per cent has been reported present in some cases It is thought that this fat passes directly from the blood through the kidney epithelium into the urine In certain types of nephritis extensive fatty degeneration of the kidney cells results in the appearance of a large quantity of non visible fat in the urine

Mechanical blocking of the lymphatic system is as a rule the cause of the more marked cases of chyluria in which the urine is opaque and whitish like milk Generally by rupturing the deeper lymphatics a leak is produced in the kidneys or bladder wall through which fat enters the urine Osler has reported a case in which obstruction of the thoracic duct was followed by rupture of the lymphatic vessels leading to the bladder Such chyluria is more marked after meals increases on reclining and is frequently associated with hematuria The simultaneous elimination of blood and fat in the urine is known as *hematochyluria*

In the *diagnosis* of nonparasitic chyluria great care must be used to exclude *Filaria bancrofti* from the possible etiologic agents

Creatinuria—The presence of creatine in the urine has not as yet been fully explained During early childhood it is normal for both sexes In the normal male creatinuria ceases permanently at about seven years of age in the female on the other hand it persists until puberty and recurs with each menstrual period during pregnancy and during *postpartum* involution of the uterus

Although many of the phenomena involved in the transformation of creatine into creatinine are known the exact metabolism and source of these substances is an unsolved problem Creatine is present in the body in large quantities the voluntary muscles contain the highest concentration the brain and testes are next in order and in the circulating blood the concentration is lowest Muscular exercise seems to have no effect upon the rate of excretion of creatine but variations in the ability of the muscles to utilize carbohydrate have a marked influence Creatine appears in the urine for instance during the muscular dystrophies and atrophies accompanied by diminished carbohydrate metabolism In such conditions as fasting or *diabetes mellitus* when the carbohydrate and glycogen depots are depleted creatinuria also occurs as well as in cancer of the liver hyperthyroidism cyclic vomiting fever certain pituitary disturbances and phosphorus and hydrazine poisoning Creatinuria has been found in eunuchs adult males with sexual underdevelopment and in most adult male and female schizophrenics It is interesting that methyl testosterone increases creatinuria while intramuscular injection of testosterone propionate decreases its excretion When occurring in hyperthyroidism it can be suppressed by large doses of vitamin C Hypoglycemia and creatinuria seem to be closely related Although the significance of creatinuria is not known careful studies have demonstrated that it is not an index of cellular destruction

Lithuria—The presence of excessive amounts of uric acid or urates in the urine is called lithuria

In man and the higher apes uric acid is the end product of the breakdown of the nucleic acid which is contained in certain protein molecules Uric acid circulates in the blood stream as a monosodium salt, for the most part in colloidal or protein combination (Benedict) It is excreted easily by the kidney in the form of sodium potassium and ammonium salts These urates form a pinkish precipitate upon standing which is soluble in urine when heated and appears under the microscope as amorphous granules Frequently however acid phosphates are present in the urine in such high concentration that the basic radical is withdrawn from these salts and uric acid precipitates in the characteristic crystals known as "cayenne pepper grains These may be colorless but are usually a rich mahogany brown because of the pigments in the urine The factors which favor precipitation of uric acid are (1) acidity (2) concentration (3) the presence of large amounts of neutral phosphate and (4) increased excretion of uric acid Both increased ingestion of foods rich in nuclein and increased catabolism of the nucleoproteins of the tissues augment excretion of uric acid

The output of uric acid decreases immediately before an attack of gout and increases greatly on the second or third day after onset

Uric acid crystals and urates frequently take part in the formation of calculi which are not opaque to x ray Uric acid crystals may cause renal colic It is interesting that excessive uric acid excretion may be unilateral

Because of a better understanding of the solubility of uric acid lithuria is considered of much less importance than formerly Prolonged alkalinization of the urine may dissolve uric acid stones

Treatment—Administration of a diet free from purine bodies which are found in meat fish liver sweetbreads brains etc removes the source of exogenous uric acid Excretion of uric acid is increased by the salicylates colchicum and especially by atophan The prolonged administration of atophan however may have a toxic effect upon the liver Ingestion of alkalis reduces the acidity of the urine and an abundant fluid intake lowers its concentration



Fig 104—Calculus of bladder The central core and outer layers are made up of calcium oxalate with ammonium magnesium phosphate filling in the middle layer (From the collection of the Department of Genito-Urinary Surgery Royal Victoria Hospital)



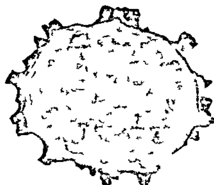


Fig 105—Cross section of the same calculus as in Fig 104

Oxaluria—Oxaluria is the presence of undue quantities of oxalic acid and oxalates in the urine

In 1838 Donne first described the calcium

oxalate crystals contained in *most acid* urine Subsequently, investigation has shown that the normal urinary output of oxalic acid (in the form of calcium salt) is between 30 to 40 mg per day The blood level averages 3 to 4 mg per cent A majority of this is derived from food but that part of it is a normal product of metabolism has been proved by the fact that during prolonged fasting the excretion of oxalic acid continues Since the *solubility* of calcium oxalate in urine is independent of the degree of acidity and depends on colloidal conditions and since urine is normally supersaturated with calcium oxalate crystals of this salt may be seen in acid, neutral and alkaline specimens

Absorption of the insoluble calcium salt which is present in most vegetables is facilitated by the hydrochloric acid of gastric juice and by excessive fermentation of carbohydrates in the intestine Calcium inhibits absorption of the salt

In certain individuals with so called oxalic acid diathesis calcium oxalate stones tend to form They usually develop first in the pelvis of the kidney and are so hard and rough as to cause frequent bleeding Crystals alone may cause hematuria frequency and lumbar pain Calcium oxalate stones have a marked density and cast an opaque shadow by x ray They may form in the bladder behind prostatic or urethral obstruction

Treatment —The purpose of treatment is to facilitate solution of oxalates in the urine by increasing its acidity with double acid phosphates raising the magnesium content and lowering the calcium content Consequently the diet should be rich in protein contain little carbohydrate and oxalic acid Rhubarb *spinach potatoes strawberries* beets tomatoes tea coffee and cocoa must therefore be avoided Acid sodium phosphate increases the acidity of the urine satisfactorily

Cystinuria —A rare disturbance of the intermediary metabolism of protein results in cystinuria—the passage *of cystine in the* urine—or in the formation anywhere in the genito urinary tract of calculi composed of *pure cystine crystals* Under normal conditions cystine which is an amino acid containing sulfur is broken down into simpler compounds but during some metabolic con*ditions it is directly* excreted More recently it has been shown that the urinary cystine comes from the protein sulfur which is present in the *protein molecule as methionine* Difficult to understand is the fact that the level of cystine excretion by a cystinuric is not increased by ingestion of cystine itself but is increased by proteins rich in sulfur

The *occurrence* of cystinuria in three generations of one family is evidence of the possibility that it is caused by some hereditary condition

Cystine was first discovered by Wollaston *in 1910 in a urinary calculus The typical* hexagonal crystals which form in the urine are soluble in concentrated mineral acids and alkalis Cystine stones are often multiple and cast a uniform shadow with x rays Unless these stones are formed, cystinuria is accompanied by no symptoms The tyrosine and leucine crystals which appear in the urine of some patients are evidence of a still more far reaching abnormality of met*abolism*

Treatment —This metabolic abnormality is a lifelong and incurable condition An alkaline ash type of diet with low protein content is indicated During cystinuria the fluid intake should be abundant, and the protein content of the diet low If a calculus has formed administration of *alkali* (6–10 Gm of sodium bicarbonate per day) is advisable and intrapelvic lavage with an alkaline solution may be helpful Such treatment is followed by disappearance of cystine crystals from the urine and complete dissolution of the stone has been reported

Phosphaturia —Normally the kidneys excrete between 1 and *5* Gm of *phosphoric* acid (P_2O_5) in the form of phosphates but *at times either* this elimination becomes excessive or the phosphates are precipitated by a change in the reaction of the urine Such abnormal excretion and precipitation is called phosphaturia *The phosphates* thus excreted are of two types the alkaline (Na K) and the earthy (Ca Mg) The most *abundant are the* sodium compounds which play an important part in the regulation of the acid base equilibrium of the body Calcium phosphate is the most important of the earthy salts

Undue precipitation of phosphates occurs when infection of the genito urinary tract

is accompanied by the excretion of alkaline urine It frequently results in the formation of stones in the bladder renal pelvis and urethra These are usually composed of crystals of ammonium magnesium phosphate calcium phosphate calcium oxalate and ammonium urate The magnesium salt is the most abundant Calcium phosphate stones are the common ones found with prostatic obstruction

During phosphaturia the urine is alkaline and cloudy when voided but clears on the addition of acid The earthy (Ca Mg) phosphates present are converted by heat into monocalcium and tricalcium phosphates These produce a fine turbidity which disappears when acid is added Phosphaturia can be unilateral and can cause attacks of renal colic

Treatment should remove any infection present and lower the intake of calcium which renders the phosphates more soluble Acid sodium phosphate should be administered in order to make the urine acid A free fluid intake is advisable Continuous irrigation for six hours per day has resulted in solution of bladder and renal pelvis calculi of this type A nonirritating citric acid solution buffered to approximately P_4 has been used

Indicanuria —The term indicanuria is applied to the appearance of indican in the urine in comparatively large quantities only for as much as 12 mg per day is excreted by the normal individual

Urinary indican is derived from the indole generated by bacterial putrefaction in the intestines The action of the colon bacillus upon tryptophan an amino acid which is present in the intestine is of special importance in this process The indole is absorbed by the blood oxidized and joined with potassium sulfate in the liver to form indoxyl and finally indican

Indicanuria is the best index of intestinal putrefaction and is most marked during obstruction of the small intestine It occurs whenever pus collects in the body as well as during peritonitis and some wasting diseases Excretion of small amounts of indican is normal in the newborn

Because of the slight toxicity of indole and indican constitutional *symptoms* do not develop until considerable quantities have been absorbed Large amounts may be related to definite clinical symptoms affecting mainly the nervous system and taking the

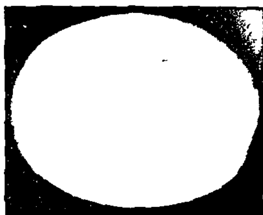


Fig 106 —Calculus of bladder composed mainly of ammonium magnesium phosphate crystals (From the collection of the Department of Genito-Urinary Surgery Royal Victoria Hospital)

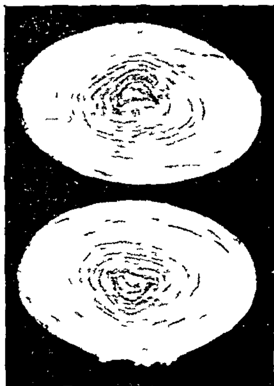


Fig 107 —Cross section of the same calculus as in Fig 106 Note concentric structure

pattern of convulsive seizures of an epileptiform type

Indicanuria is demonstrated by a simple test which consists of the addition of a strong oxidizing agent and subsequent shak

ing with chloroform The indigo which forms from indican (potassium indoxyl sulfate) in the presence of the oxidizing agent gives its characteristic blue color to the solution containing chloroform

Treatment should consist of limiting the meat and increasing the milk intake Lactose inhibits the growth of putrefaction organisms Acidophilus milk has been helpful In the case of achlorhydria hydrochloric acid by mouth will favor a more complete digestion of meat

Melanuria —In certain pathologic conditions the production of excess melanin, the normal coloring matter of the skin hair and choroid of the eye, results in the appearance of this pigment in the blood and urine *i e* in melanemia and melanuria This occurs during the course of Addison s disease and also in rare cases in which local degeneration of the tissues of melanotic tumors liberates large quantities of melanin In the latter case as much as 500 Gm may be present in the body Melanin is normally very abundant in the skin of the black races and it has been estimated that the skin of a single individual may contain 1 Gm

Probably the *source* of the several closely related bodies now classified as melanin is to be found in certain chromogen groups of the protein molecule and not in hemoglobin

Although urine which contains melanin may be darkly colored when voided its appearance is usually normal This is explained by the fact that the melanin circulating in the blood is reduced by the liver to colorless *melanogen*—a substance which turns black when exposed to air or to other oxidizing agents Urine may be colored dark brown by only 0 1 per cent of melanin

According to Helman the presence of true melanogen in the urine can be determined by three reactions the precipitation of a black substance on the addition of ferric chloride the solution of this substance in the presence of sodium carbonate to form a black solution and the formation of a black or brownish powder when mineral acid is added to the black carbonate solution All of these tests must be positive before melanogen can be said to be present

Alkaptonuria —Alkaptonuria or the presence of alkaptone (homogentisic acid) in the urine is rare generally persists throughout life, and is more common in the male than in the female It is the result of a harmless anomaly of the intermediary protein metabolism which appears to bear some relation to the recessive characters of mendelian inheritance First cousin marriages have frequently produced alkaptonuric offspring

Although the *clinical manifestations* of alkaptonuria were well described by Marcet in 1823 the presence of alkaptone or homogentisic acid in the urine was not recognized until 1887 At this time Marshall isolated the substance in the urine but called it glycosuric acid Its principal precursors are the tyrosine and phenylalanine of the protein molecule Relatively as much is produced by endogenous protein as by that contained in the food although of course the actual quantities derived from the two sources are of very different magnitude Normally alkaptone is broken down by the tissues of the body—probably by the liver alone—before excretion but in certain individuals it may be isolated in the circulating blood and is eliminated in the urine as an ammonium salt Experimental work on white rats has indicated that homogentisic acid is an intermediate product of the normal metabolism of phenylalanine It is interesting to note that light is given off during the oxidation of homogentisic acid in alkaptonuric urines This light is visible as a faint glow in the foam after shaking This fact may explain certain luminous urines reported in the early literature

Urine which contains alkaptone stains the linen tends to turn dark when exposed to the air and is frequently dark when voided If mixed with an alkali it becomes black The addition of dilute ferric chloride solution drop by drop produces a transitory blue coloration Such urine reduces Fehling s solution atypically does not ferment and is optically inactive

In rare cases of alkaptonuria the cartilages turn dark (ochronosis) and there is a tendency to the development of chronic arthritis Since nonspecific fixation of the blood is often associated with the excretion of homogentisic acid great care must be used in interpreting the Wassermann reaction when patients are known to be alkaptonuric

Treatment—As a rule there are no subjective symptoms which require treatment Fluids should be taken freely, and if desirable the quantity of alkaptone in the urine may be reduced by decreasing the protein content of the diet Klein and Block have reported that intramuscular injections of liver extract freed the urine of homogentisic acid for eight to ten hours after a four to six hour interval

Pneumaturia.—Pneumaturia is the passage of gas with the urine It is known to occur after irrigation of the bladder and following cystoscopic examination of patients in the knee-elbow position as well as during chronic cystitis When the gas is derived from an extraneous source its appearance in the urine is only temporary for elimination is hastened by rapid absorption into the blood Intravesical generation of gas is most common during chronic cystitis and is caused by gas forming organisms—the colon bacillus the yeast fungus or the *Bacillus aerogenes capsulatus* In such cases the urine is foamy when voided and usually contains sugar Rarely vesico intestinal fistulae secondary to carcinoma of the sigmoid ruptured diverticulum of the descending colon or sigmoid or *diverticulitis* are associated with a cystitis of this type

The *symptoms* are usually those of mild cystitis The urine may be foamy when voided or the gas may be passed at the end of micturition

Pneumaturia may be demonstrated by the passage of urine under water or by submerging the end of the catheter

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PAROXYSMAL HEMOGLOBINURIA

Definition.—Paroxysmal hemoglobinuria is a rare disease characterized by transitory hemoglobinuria following exposure to cold or occasionally after exertion and by the presence in the blood of an autohemolysin which unites with the red blood cells only at low temperature The disease is a manifestation of late syphilis either congenital or acquired

History—In 18?4 Dressler wrote about "intermittent albuminuria and chromaturia," and set forth the first good description of paroxysmal hemoglobinuria. During the last half of the nineteenth century numerous reports appeared The clinical features were well defined and the disease soon became generally recognized as an entity Donath and Landsteiner (1904) made an important contribution when they observed that the blood of these patients contains an autohemolysin which may be demonstrated by a simple *in vitro* test.

Etiology—Syphilis is now accepted as the essential cause of the disease The paroxysmal hemoglobinuria may or may not show other signs of late syphilis but the Wassermann reaction is almost invariably positive Nearly all of the reported cases have occurred either in children with congenital lues or adults long past the secondary stage of acquired syphilis The characteristic autohemolysin may be found in certain other syphilitics especially in patients with general paresis who have not had hemoglobinuria

Pathology—Although paroxysmal hemoglobinuria is intimately related to late syphilis it is possible by appropriate methods to remove from the blood the *autohemolysin* without weakening the Wassermann reaction The titer of the autohemolysin in the serum may show variation from day to day it may persist after the patient has ceased to have paroxysms upon exposure to cold In the serum from different patients it shows varying degrees of thermolability The writer has studied one patient whose

autohemolysin was destroyed at 47.5° C for thirty minutes so that fresh complement failed to reactivate it A specimen from another patient was not destroyed at 55° C for thirty minutes The blood of the paroxysmal hemoglobinuric contains an isohemolysin probably identical with the autohemolysin, at least efforts at separation have been unsuccessful

The *Donath and Landsteiner phenomenon* reveals one of the fundamental features of the mechanism which operates during a paroxysm The test tube reaction in its simplest form is carried out by chilling the patient s blood to about 5° C for ten minutes and then warming it to 37° C, when hemolysis occurs Normal blood so treated shows no hemolysis Since the reaction requires complement which in human blood is usually not abundant more constant results are obtained if one separates the serum makes a suspension (5 or 10 per cent) of the red blood cells and adds fresh guinea pig complement In the test tube reaction more hemolysis occurs if a heavy suspension of red blood cells is used and if the chilling is of short duration—seven to ten minutes rather than thirty to sixty minutes Slight union of the autohemolysin with the corpuscles may occur at a temperature as high as 16° C With lower temperatures the union is more complete

In the spontaneous paroxysm it seems quite probable that blood in superficial capillaries might be chilled to 15° or 16° C Union of the autohemolysin and red blood cells would then occur In the presence of complement hemolysis results after the chilled blood has passed from the surface of the body to the higher temperature of internal blood vessels Hemoglobinuria follows It has been shown however that attacks can be artificially produced by exposing the surface of the patient s body to a temperature (18° C) higher than the highest temperature at which union of the hemolysin and the red blood cells can be demonstrated *in vitro* The urinary findings occur whenever the free hemoglobin in the blood rises above the renal threshold of hemoglobin excretion In case the hemolysis is so slight that the renal threshold is not exceeded an abortive paroxysm occurs—hemoglobinemia with mild symptoms and no hemoglobinuria the so called "*petit mal* of hemoglobinuria The appearance of urobilin in the blood results from the increase of free hemoglobin the precursor of bile pigments which in turn constitute the mother substances of urobilin Extrahepatic formation of bile pigment or excessive production in the liver explains the slight jaundice not infrequently seen following the paroxysm Recently Harris Lewis and Vaughan have demonstrated a dermolysin in the plasma of one of these patients The dermolysin united with the cells of the skin only at low temperatures subsequent warming of the skin caused edema and urticaria The skin of syphilitic patients without paroxysmal hemoglobinuria could be passively sensitized to cold by intracutaneous injections of dermolysin containing serum

Symptoms—Between the chilling which may be surprisingly slight and the onset of the paroxysm there is a *latent period* varying from a few minutes to six or eight hours During this time the leukocyte count may drop to 2000 or 3000 with a relative increase in lymphocytes With the onset of the attack the number of lymphocytes decreases and a slight polymorphonuclear leukocytosis occurs The attack consists of malaise often headache pain in back and legs or abdomen chilly sensations or a shaking chill, transitory fever during which the temperature may be 104° F or higher and cyanosis Some patients show a temporary rise in systolic and diastolic blood pressures of 50 to 100 mm of mercury Frequently the liver and spleen enlarge during an attack In a few cases the phenomena of Raynaud s disease are associated with the attacks or other manifestations of vasomotor disturbance such as urticaria or vesicular lesions The urine is dark red or Burgundy color often described as black by the patient It contains hemoglobin methemoglobin hematin and hyaline granular and pigment casts and urobilin The presence of the pigment uro erythrin has also been demonstrated In these cases the urine is rose colored In freshly passed specimens intact erythrocytes may be found The hemoglobin may be present in only one specimen of urine or it may persist for a day or two Following the attack *mild jaundice* is common In the interval between attacks the

patient may be in good health but not infrequently there are symptoms due to other manifestations of late syphilis When attacks have been repeated at short intervals *secondary anemia* is commonly present

Diagnosis —The history of transitory excretion of dark colored urine during the winter months following exposure to cold or exertion a positive Wassermann reaction and stigmata of late syphilis the Donath and Landsteiner reaction in the drawn blood and the artificial production of an attack by immersion of hands or feet in ice water provide the data which establish diagnosis Without a positive Wassermann reaction the diagnosis is uncertain because there are other types of transitory hemoglobinuria unassociated with syphilis for instance the *Marschhamoglobinurie* (Fleischer, Schellong) in which the paroxysm is induced by a long march or walk The writer has observed one case of this type in a college student A brisk walk of several miles sufficed to bring on a paroxysm of hemoglobinuria with hemoglobinemia similar to the attacks of the syphilitic hemoglobinuric His health was otherwise excellent other forms of exercise were without effect there was no evidence of syphilis the blood did not give the Donath and Landsteiner reaction Another type of hemoglobinuria to be differentiated is the *chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria* (Micheli Marchiafava Witts Hamburger and Bernstein) This recently recognized disease known as the Marchiafava Micheli syndrome is characterized by paroxysms of hemoglobinuria persistent hemoglobinemia and anemia between attacks absence of relationship between exertion or chilling and the hemoglobinuria tendency of the attacks to occur at night reticulocytosis urobilinuria hemosiderinuria and incurability The hemoglobinuria of chronic malaria is also to be differentiated

Treatment —Various forms of therapy have been advocated autoserotherapy (Widal Abrami and Brissaud) graded cold foot baths (Salen) and administration of calcium chloride or calcium lactate These forms of treatment lack a rational basis and have not been demonstrated to compare in effectiveness with *antisyphilitic treatment* which Kumagai and Namba in a study of 14 patients have clearly shown to be the method of choice The writer has observed two patients who after thorough antisyphilitic treatment passed through two consecutive winters in New York without an attack In each case however the Wassermann and the Donath Landsteiner reactions remained positive though weakened The patients were treated with many arsphenamine injections mercury, iodides and bismuth This result corroborates the observations of Jones and Jones

George M Mackenzie

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NEPHRITIS

(*Bright s Disease*)

Introduction —In 1836 Richard Bright wrote 'It is indeed an humiliating confession that although much attention has been directed to this disease for nearly 10 years yet little or nothing has been done toward devising a method of permanent relief when the disease has been confirmed and no fixed plan has been laid down as affording a tolerable certainty of cure in the more recent cases '

A hundred years later we must amplify this apology of Bright with the equally humiliating confession that we today cannot cure the disease Furthermore its etiology and the mechanism of its progression or of spontaneous healing remain ob

scure Finally, the establishment of its diagnosis is at times impossible Hence a textbook discussion of Bright s disease must in part be indefinite in its statements unsatisfactory as to the statistical study of its incidence course and outcome, and speculative concerning its nature and the therapeutic measures to be employed Despite this apparent state of confusion and in all fairness to the innumerable studies devoted to the subject of nephritis it should be recognized that the importance of the relationship of certain infections to the onset and course of the disease has in a measure been clarified Also the development and application of *quantitative biochemical methods have contributed* enormously to our understanding of the pathologic physiology of Bright s disease upon which is based rational therapy

Definition —The term 'nephritis embraces a number of disease states of unknown etiology which may be acute or chronic and all of which are characterized by albuminuria and cylindruria and often by hematuria In addition to these signs of local renal dysfunction which are dependent upon bilateral nonsuppurative inflammatory or degenerative kidney lesions edema hypertension and nitrogen retention are frequently present Many of the manifestations both local and systemic are referable to disturbances in the vascular system

Classification —The present status of the classification of nephritis has been best described by Addis who says "Every student of Bright s disease constructs his own classification to meet his own individual interests and needs" In the absence of an etiologic basis for the classification of Bright s disease most terminologies have been of a descriptive clinical or anatomic nature Among the former various authors have divided the nephritides into those with or without edema while others have spoken of 'salt and water retention nephritis and 'nitrogen retention nephritis' These distinctions can no longer serve a useful purpose as we now know that these terms apply merely to different phases of a single disease process often encountered in the same patient The same may be said of classifications which attempt to differentiate various forms of nephritis by the predominance of manifestations resulting either from decreased blood flow through the kidney or from disturbances of filtration in the glomeruli and of reabsorption by the tubules Classifications based upon anatomic changes in the kidneys have fared better and are more generally accepted but they also have serious limitations Their greatest drawback is the fact that the pathologist not infrequently is unable to determine the nature or picture the course of the antecedent disease on the basis of the gross or microscopic findings present at death With the present limitations of our knowledge the chief aim in developing a classification is to find terms which may for the time being serve as labels *characterizing for the pathologist and clinician* the general aspects of Bright s disease in its various forms The following classification in simplified form is that which is in common usage today and the terminology must be recognized as being more specific than is justified by clinical and histopathologic knowledge In the light of the foregoing discussion it must be considered purely tentative

(*A*) Glomerulonephritis
  1 Acute form
  2 Chronic form
(*B*) Arteriolar nephrosclerosis
(*C*) Nephrosis
(*D*) Miscellaneous nephritides

Consideration of the various subdivisions of these larger classes will follow in their respective sections

GLOMERULONEPHRITIS

Etiology —Although the etiology of acute glomerulonephritis remains unknown all recent studies indicate clearly that a close relationship exists between certain infections and the onset of the disease In a vast majority of instances acute nephritis follows *infection of the upper respiratory tract* and in cases where careful bacteriologic and immunologic observations have been made it has become apparent that the hemolytic streptococcus (Group A of Lancefield) above all other organisms is of *prime importance* For example Longcope reported the presence of hemolytic streptococcal infection in 85 per cent of the patients with acute nephritis studied by him In the series of Seegal Lyttle E N Loeb and Jost the

sera in seventy six of eighty consecutive patients with acute nephritis contained a sufficiently high titer of antistreptolysin to be indicative of a recent hemolytic streptococcal infection From these observations and many similar ones we find that disease of the upper respiratory tract be it tonsillitis pharyngitis sinusitis the common cold grippe' peritonsillar abscess scarlet fever rheumatic fever etc is usually associated with streptococcal invasion when it is followed by acute glomerulonephritis Further evidence attesting to this relationship is the seasonal variation in acute nephritis found by Seegal *et al* The curve of incidence of acute glomerulonephritis in patients seen in the Presbyterian and Babies Hospitals in New York parallels closely that of streptococcal infection It should be pointed out however that it is not necessary for streptococcal infection to enter the body by the respiratory tract in order to have an associated acute nephritis for a number of cases probably more than are generally appreciated follow skin or wound infection by that organism In acute rheumatic fever, a disease in which the hemolytic streptococcus admittedly plays an important role about 15 per cent of the patients have either gross or microscopic hematuria In spite of this curiously enough only three of about 100 of Coburn s cases which were examined post mortem showed the presence of acute glomerulonephritis It seems likely that the renal bleeding so frequently encountered is not the result of glomerular inflammation but is merely another manifestation of the hemorrhagic diathesis in the rheumatic state On the other hand 25 per cent of patients dying with acute nephritis at the Presbyterian Hospital were shown at autopsy to have associated active rheumatic disease

That the streptococcus is not invariably *the infective agent* associated with the onset of acute nephritis seems apparent from the fact that most observers have a number of cases in their series which are thought to be associated with pneumococcal or gram negative coccal infections various pyogenic infections enteric fevers or with no demonstrable infectious process at all It must be kept in mind however that in many of these cases the presence of associated hemolytic streptococcal infection has not been eliminated by adequate bacteriologic or immunologic methods Despite this criticism it is certain that infectious agents other than the hemolytic streptococcus are occasionally associated with the onset of acute nephritis The disease picture in postpneumonic nephritis differs sufficiently from the usual type of acute nephritis to give this idea special support For example hypertension is usually absent even as uremia appears anemia is rapidly progressive and an increase in the antistreptolysin titer of the serum is absent

In addition to the factors already mentioned certain *chemical poisons* such as turpentine carbon tetrachloride cantharides arsenic and chromium salts cause renal irritation but this does not resemble the clinical or pathologic picture of acute glomerulonephritis On the other hand when sulfapyridine sulfathiazole and less frequently sulfadiazine have been administered hematuria oliguria nitrogen retention and edema may appear and at times these drug effects are indistinguishable from nephritis which might be induced by the underlying infection The confusion concerning the nature of the toxemias of pregnancy is so great that their consideration contributes little or nothing to a discussion of glomerulonephritis Bacterial endocarditis and other septic states are not infrequently associated with embolic and local inflammatory lesions in the kidneys and occasionally typical glomerulonephritis is superimposed on these lesions This is most frequently seen in cases of infection with *Streptococcus viridans*

The foregoing discussion has dealt with the *etiology* of *acute* glomerulonephritis in which the intimate association of this disease with hemolytic streptococcal infection has been stressed Nevertheless the severity and the course of the nephritis are entirely independent of the severity of the preceding infection The role of acute infectious processes in the etiology of *chronic* glomerulonephritis is much less certain although an exacerbation of the disease accompanies or follows intercurrent streptococcal infection not infrequently In the studies of Seegal *et al.* one or more exacerbations were seen in thirteen of a series of sixty eight patients observed from one to eight years In all bacteriologic or immunologic evidence indicated that the exacerbation may be initiated

by streptococcal infection but in five of twenty eight exacerbations no evidence of streptococcal infection was obtained The usual insidious onset and its lack of correlation with definite episodes of infection in striking contrast to the acute disease make it seem possible although not probable, that chronic glomerulonephritis may differ from the acute form not only in its mechanism and course but also in its etiology While certain investigators are of the opinion that the chronic form of glomerulonephritis results, as a rule, from the persistence or from frequent recurrence of overt or subclinical infection with the hemolytic streptococcus the evidence for this idea is not wholly convincing If hemolytic streptococcal infection be the usual cause of *chronic glomerulonephritis then the immune* response of the patient to that organism as measured by the anti streptolysin titer of his serum is different from that seen in the acute form The antistreptolysin titer in the acute form is elevated, frequently to extraordinarily high levels whereas in the chronic stage it is ordinarily low Outspoken streptococcal infection in these patients may cause the antibody titer to rise but not to the usual levels seen in acute nephritis Our ignorance concerning the etiology of chronic glomerulonephritis is well illustrated by the fact that the simple question of the frequency with which acute nephritis becomes chronic is answered by investigators in the field with the greatest divergence of opinion For example Addis, and also Longcope states that more than 40 per cent of patients suffering from acute nephritis develop the chronic form of the disease whereas Richter and others find the acute disease progressing in less than 20 per cent Still more confusing is the experience of Snoke This writer states that among a large series of children with acute nephritis studied by him in California the incidence of progression to the chronic form of the disease was 39 per cent In studying a similar group of children in Rochester New York he found progression from the acute to the chronic form in only 10 6 per cent

Mechanism of Glomerulonephritis—In the foregoing discussion the frequent association of infection with the onset of acute glomerulonephritis has been emphasized but this knowledge has not fundamentally advanced our understanding of the mechanisms involved in the production of the disease Thus many important and intriguing questions remain unanswered

Bacteriologic studies of recent years have shown conclusively that actual invasion of the kidneys by the infectious agent does not occur in acute or chronic glomerulonephritis except in the presence of bacterial endocarditis or sepsis Furthermore evidence points against the concept of immediate damage to the kidneys by the bacterial products because of the fact that acute glomerulonephritis almost invariably follows rather than accompanies the acute infection For example the acute nephritis of scarlet fever develops classically ten to twenty days *after the onset of the exanthem and a con*siderable time after the subsidence of the febrile reaction Similar time relationships obtain in acute nephritis following tonsillitis and other infectious processes In 1912 Escherich and Schick expressed the view that this time relationship suggested the possibility that glomerulonephritis was not induced by infection *per se* but by the immune reactions resulting from the infection Since that time Friedmann Longcope and others have come to a similar conclusion This concept may offer a satisfactory explanation for some of the obscure phenomena observed in the disease and is at the present time receiving support from laboratory investigation

Many attempts to produce in animals disease pictures analogous to acute and chronic glomerulonephritis in man have failed or have proved to be inconclusive In 1928 Masugi demonstrated that an antikidney serum produced by the injection of rat kidney emulsion into rabbits when injected into rats gave rise to acute or chronic nephritis These observations were confirmed by Arnott *et al* and have been greatly extended by Smadel and Farr The latter have shown that the injection of one two or three doses of rabbit antirat kidney serum into rats in the course of a few days induces acute nephritis Some of the animals so treated recover in about three weeks while others develop chronic nephritis which in the course of many months becomes associated with edema hypertension anemia

nitrogen retention and marked decrease in renal function The lesions in this latter group of animals treated with nephrotoxic kidney antisera bear a close resemblance to chronic glomerulonephritis in man These are striking and significant observations in asmuch as they demonstrate that a single insult to previously normal kidneys may initiate chronic progressive renal disease Smadel and Farr have recently found that in one strain of rats the course of the disease initiated by nephrotoxic immune serum may be altered by the amount of protein in the diet If this be restricted the nephritis tends to heal whereas if the amount of protein in the diet be increased the nephritis becomes progressive Thus the question of the possible deleterious effect of large amounts of protein stressed by earlier workers is again raised

If these observations concerning the nephrotoxic action of antikidney sera be applicable to man we can hypothesize that an infectious agent such as the hemolytic streptococcus produces within susceptible individuals nephrotoxic immune bodies These may then give rise to acute or chronic glomerulonephritis It is in relation to the latter form that we may find in these laboratory studies a possible explanation for those cases of progressive chronic glomerulonephritis in which most rigid clinical bacteriologic and immunologic studies fail to produce evidence for the persistence or recurrence of streptococcal infection to account for the relentless progression of the disease Unfortunately none of the experimental studies throws light on the obscure fact that most cases of chronic glomerulonephritis begin insidiously and without apparent relation to a recognized preceding infectious process The foregoing highly speculative discussion has no practical application but shows the trend of present day thought in relation to the mechanism of one of the commonest and most obscure of human maladies

Predisposing Factors—The role of sex in the susceptibility to glomerulonephritis is of interest in that there is a striking consistency in the preponderance of the disease among males in a ratio of approximately 2 1 No satisfactory explanation is offered for this unequal distribution

Age—Glomerulonephritis is essentially a disease of children and adults in the earlier decades of life the acute form being more common in children than in adults The Seegals and Lyttle reported that 70 per cent of their cases occurred before the age of twenty one The *incidence* of the disease in the acute form cannot be determined with any degree of accuracy because those patients without extrarenal symptomatology frequently do not come to the attention of a physician, and even when they do there is difficulty in establishing the diagnosis in these mild forms Among the cases diagnosed in general hospitals the Seegals and Lyttle found that among 35 000 admissions to medical wards the incidence was 0 02 per cent in northern hospitals while in hospitals of Louisiana and Texas the incidence was approximately the same being 0 47 per cent Since the disease in its chronic form so frequently begins insidiously the proof of its relatively early onset in life is best established by the age at death Of fifty seven autopsied adult cases at the Presbyterian Hospital thirty five died before the age of forty In a similar group but including children Fishberg reports that forty two of fifty four patients also died before the age of forty

Climate—As mentioned above the incidence of acute glomerulonephritis has been found by the Seegals to be independent of latitude These same investigators found that in the southern states as well as in the north the disease reaches its greatest incidence at that season of the year when disease of the upper respiratory tract and streptococcal infection are at a peak

Exposure to Cold—Many years ago the role of exposure to cold was thought to have great significance in relation to the onset of acute nephritis These instances became progressively fewer perhaps because the time interval between infection and the appearance of nephritis is better appreciated and because more careful bacteriologic and immunologic studies are made

Familial Susceptibility—Nine of fifty seven patients at the Presbyterian Hospital who came to autopsy because of chronic glomerulonephritis gave a family history of Bright s disease Ernstene reported a family in which six of ten children developed acute glomerulonephritis secondary to upper respiratory infection In spite of these facts the

familial incidence appears low in contrast to that present in arteriolar nephrosclerosis

Morbid Anatomy—At autopsy, the kidneys in *acute glomerulonephritis* are normal in size or slightly enlarged They are usually pale in color and may show punctate hemorrhages on their smooth surfaces On section the demarcation between cortex and medulla is well preserved and the glomeruli may appear as pale or hemorrhagic dots Microscopically, the earliest changes suggest an inflammatory lesion of the capillary loops in the glomeruli The endothelial cells are swollen and they proliferate and cause the glomeruli to become ischemic Later proliferation of epithelium outside of the capillary begins and polymorphonuclear cells accumulate in the glomeruli Thus the tufts appear rich in cells and in time tend to fill the capsular space completely In many of the glomeruli there is hemorrhage into the capsular space and also a deposition of fibrin The cells of the *tubules* show varying degrees of swelling and fatty deposit and their lumina are often filled with blood leukocytes and cellular debris The interstitial tissue tends to be edematous its capillaries are congested and scattered leukocytes are present The arterioles usually show little or no change but occasionally the glomerular inflammatory process is associated with an acute necrotizing arteriolitis

If acute glomerulonephritis heals there is usually no trace of it found at autopsy when death occurs from some other cause On the other hand if the process does not heal the disease progresses in the course of a few weeks or months to that intermediate phase which the clinician hesitates to call chronic but which is too prolonged and too continuously severe to be compatible with the acute stage This phase is known as *subacute glomerulonephritis* The kidneys are pale and swollen and constitute what were formerly called large white kidneys The surface is still smooth and has a fatty or grayish color Punctate or striate hemorrhages are still numerous and on section the cortex seems unusually wide and merges indistinctly with the medulla Microscopically the *glomeruli* show further increase in their cellular content or the capillaries are dilated with blood The capsular spaces contain blood and cellular debris and the capsule shows proliferation of the epithelial elements to form the so called ' epithelial crescents The cells of the *tubules* show further swelling and many have an accumulation of large fat droplets This degenerative change is associated with desquamation of the tubular epithelium There is an increase in cellular infiltration mostly lymphocytes in the *interstitium* and arteriolar changes are variable With further progression of glomerulonephritis the *chronic* form is reached which in a period of from one to forty years becomes terminal This chronic state is characterized by further gross and microscopic changes in the kidney The kidneys contract and are frequently reduced to one fourth their normal size The capsule is adherent and the surface pale and granular On section the cortex is markedly narrowed Microscopic examination shows progressive hyalinization and disappearance of the glomeruli Some of the tubules collapse and disappear though others become cystic Fibrosis of the interstitium is progressive and the arterioles show varying degrees of sclerosis In many instances the arteriolar changes become sufficiently striking to make it impossible to state from postmortem examination alone whether they are secondary to glomerulonephritis or whether the glomerular changes have followed arteriolar nephrosclerosis

ROBERT F LOEB

ACUTE GLOMERULONEPHRITIS

Clinical Picture—The classical' picture of acute glomerulonephritis is seen frequently in children and in young adults following infection with the *Streptococcus hemolyticus* The patient usually complains of hematuria puffiness of the face headache and a decrease in urinary output In the fulminating form of the disease edema may become generalized visual disturbances may occur hypertension may become extreme dyspnea marked delirium convulsions coma and death may ensue This dramatic sequence of events may be accompanied by fever anorexia vomiting anuria and varying degrees of nitrogen retention The foregoing description comprises perforce a com

posite picture of the more striking features of acute glomerulonephritis However it should be emphasized that the "classic" *i e* the unmistakable picture is rarely encountered in medicine More frequently one or more symptoms or signs dominate the disease For example in many patients with acute nephritis edema may be the only complaint or objective physical finding In others gross hematuria alone may attract attention to the disease A few complain of weakness or of backache In still others it is important to recognize that there may be no symptoms and no abnormalities on physical examination or they may be so mild and transient in nature that they entirely escape detection The diagnosis in these cases which are numerous is made possible only by the examination of the urine

In Richter s series *edema* was present in two thirds of the cases of acute nephritis It usually begins about the eyes and the face becomes puffy and pasty in appearance This is frequently most apparent when the patient awakes in the morning In many cases the edema involves the dependent parts and in some it becomes generalized occasionally being accompanied by effusion into the serous cavities it usually appears early in the disease though it may appear at any time The development of edema is due to at least three factors (1) A decrease in urine formation from a decreased blood flow through the ischemic glomeruli (2) Increased capillary porosity resulting from generalized capillary damage allowing the abnormal escape of fluid rich in protein to the interstitial spaces This in turn lowers relatively the effective osmotic pressure of the blood thereby tending to increase edema (3) Elevation of hydrostatic pressure by congestive heart failure contributing to edema formation in a number of cases It is of interest that the serum protein level in acute nephritis with edema is rarely reduced below 5.5 per cent although the albumin fraction may be significantly lowered

Variations in the elevation of *blood pressure* in acute nephritis are great The pressure may never exceed normal limits in the entire course of the disease On the other hand in about 25 per cent of the cases there is a moderate transient elevation of either the systolic or diastolic pressure or both In about 10 per cent the systolic pressure reaches 180 to 200 mm mercury and the diastolic pressure may be maintained well above 110 mm mercury In seven studied cases of postpneumonic nephritis Seegal has pointed out an absence of hypertension

In acute nephritis the elevation of blood pressure like the development of edema usually begins early in the disease but may appear some time after the onset Progressive elevation of pressure usually precedes the appearance of cerebral and cardiac symptoms The pressure may fluctuate widely from day to day suggesting that arteriolar spasm is probably the chief underlying mechanism involved In a few cases an extreme degree of hypertension is associated with an acute necrotizing arteriolitis

Closely allied with changes in blood pressure in acute nephritis are the *cerebral manifestations* of the disease When the pressure begins to rise rapidly there may develop severe headache nausea and vomiting somnolence or mental confusion Finally generalized clonic convulsions may occur These episodes were present in 10 per cent of the series studied at the Peter Bent Brigham Hospital Their mechanism is not understood but they are not dependent upon nitrogen retention They are probably due in part to cerebral ischemia associated with arteriolar spasm and hypertension and with more or less cerebral edema Convulsions may occur once or they may recur at frequent intervals as in a status epilepticus Death is not uncommon following recurrent convulsive seizures *Visual disturbances* occur with these attacks of so called hypertensive encephalopathy The commonest of these is blurring of vision Amaurosis is transient in nature and occurs in about 2 per cent of hospital cases The *eyegrounds* in acute nephritis are usually normal but many changes may occur Papilledema is not unusual and is most frequently seen with elevation of blood pressure with or without hypertensive cerebral episodes The retinal arteries appear pale and narrow when hypertension is marked Hemorrhages into the retina are not unusual and are probably an other manifestation of general capillary damage in acute nephritis Exudate is rarely present Occasionally the complete picture

of edematous disks vascular changes hemorrhages and exudate is seen in the fundi of patients with acute nephritis The author has seen one patient who had acute nephritis associated with massive edema hyper tension nitrogen retention a series of epileptiform convulsions papilledema retinal hemorrhages and macular stars of exudate Fourteen years later that individual had no evidence of nephritis or hypertension and his eyegrounds were normal but for slight pallor of one optic disk While such cases are distinctly unusual they occur with sufficient frequency to show that these extreme changes are at times reversible

The *heart* frequently suffers to a greater or lesser degree in the majority of cases of acute nephritis Whitehill Longcope and Williams found that myocardial failure varies in its severity in direct proportion to the severity of acute nephritis Thus fifty three of fifty nine patients with severe nephritis had some evidence of cardiac insufficiency Among mild cases twelve of thirty five had some circulatory disturbance The abnormalities encountered range from mild electrocardiographic disturbances without symptoms to extreme congestive failure associated with dyspnea orthopnea tachycardia gallop rhythm pulmonary congestion and elevation of venous pressure A number of patients with acute nephritis die from cardiac insufficiency Fatal insufficiency may be precipitated by the exertion associated with convulsive seizures

With the progressive development of massive edema fluid may collect in the pleural cavities and the *lungs* may show the presence of rales at the bases The patient may become dyspneic because of decreased lung elasticity When cardiac insufficiency supervenes frank pulmonary edema as has been mentioned may occur Edematous patients not infrequently develop secondary bronchopneumonia

The presence of *anemia* early in the course of acute nephritis is distinctly unusual and when present it should arouse suspicion of a chronic process with a superimposed acute exacerbation When acute nephritis persists over a period of many weeks particularly if renal bleeding plays a prominent role varying degrees of secondary anemia may develop The white cells in acute nephritis are normal unless infection complicates the picture

The *urine* volume in acute nephritis may be normal throughout the course of the disease On the other hand it may decrease in amount abruptly at the onset of the disease and may present either a smoky or definitely bloody appearance Anuria occurs in about 5 per cent of hospitalized patients with acute nephritis and is a serious manifestation The oliguria encountered may not be associated with outspoken edema for some time although it represents retention of fluid in the interstitial spaces The reasons for the appearance of oliguria and anuria are those mentioned in the discussion of edema In addition it seems that arteriolar spasm with a resulting decrease in blood flow through the kidneys is an important contributing factor This idea receives support from the fact that the termination of anuria and the gratifying appearance of diuresis may be sudden and too rapid to be explained by the subsidence of inflammatory lesions There is usually little interference with the ability of the kidneys to concentrate in acute nephritis and consequently the *specific gravity* of the urine is as a rule maintained at normal levels *Albumin* is regularly present in the urine in acute nephritis and the diagnosis of the disease is untenable in its absence The amounts present are extremely variable and the course and prognosis are entirely independent of them Albuminuria is frequently the last manifestation of the disease to disappear in the process of healing

Hematuria either gross or microscopic is present in acute glomerulonephritis with such regularity that the disease in the classification of Addis has been termed acute hemorrhagic nephritis In the absence of gross or microscopic hematuria the diagnosis of acute glomerulonephritis must be held in doubt The amount of blood in the urine is extremely variable In about 40 per cent of the cases gross hematuria is recognized This symptom is present as a rule for only a few days but may recur from time to time in the course of the disease Microscopic hematuria often persists for months and may continue long after routine examination fails to reveal albuminuria although as stated above in other cases al

bumin is the last to disappear A moderate number of leukocytes are usually present in the sediment but frank pus is not encountered Casts of various kinds are always present in acute nephritis Most characteristic and important diagnostically, if present among these formed elements are red blood cell casts Nevertheless other cellular casts granular hyaline and waxy casts may be present in varying numbers

Renal function as measured by tests other than routine urine examination is normal in about 50 per cent of patients with acute glomerulonephritis In others varying degrees of nitrogen retention are observed but the blood urea nitrogen rises above 100 mg per cent in less than 5 per cent of the cases The higher values are usually associated with oliguria and hypertension but it should be emphasized again that the convulsions of hypertensive encephalopathy occur independently of azotemia and may be fatal without any nitrogen retention When nitrogen is retained in appreciable amounts there may be a decrease in the rate of excretion of phenolsulfonphthalein and the urea clearance test may show a striking decrease in kidney function Accompanying these marked changes there may be retention of creatinine and uric acid and the development of acidosis due to phosphate and sulfate retention Only 2 or 3 per cent of patients with acute nephritis die of true uremia. The marked depression of renal function occurring in a number of cases is not necessarily associated with progressive disease or death On the contrary it is usually a reversible disorder which may disappear in the course of a few days as blood flow through the glomeruli increases

Diagnosis —In the classic case of acute glomerulonephritis diagnosis affords no difficulty However when albumin casts and red blood cells appear in the urine in unmistakable but small quantities after or during an acute infection with the hemolytic streptococcus or other organisms and unaccompanied by edema hypertension or nitrogen retention the problem becomes more difficult Certain authors escape this diagnostic difficulty by applying the term focal nephritis to these cases In the writer s opinion this does not advance our knowledge or clarify the situation If the urinary findings described persist over periods of one or two weeks it seems likely that acute glomerulonephritis is present If the microscopic hematuria casts and albumin disappear in a shorter time it is best to admit that the diagnosis remains in doubt and that the findings may result from increased permeability of renal capillaries due to irritation" passive congestion embolic phenomena or to causes unknown It should be emphasized that numerous blood pressure determinations repeated urine examinations and a careful record of body weight aid tremendously in detecting transient abnormalities which may establish the diagnosis in mild cases

The difficulty in establishing a diagnosis in borderline cases is emphasized by the studies of the urine in scarlet fever carried out by Lyttle This investigator applied to sixty-eight patients with scarlet fever Addis quantitative method for the determination of protein casts and cells in the urine He found in all the cases that a moderate transient increase in all elements above accepted normal levels occurred between the eighth and the forty fifth day after the onset of the disease Lyttle found similar changes in the urine following other forms of streptococcal infections but not with any regularity after infection due to other organisms To state on the basis of these findings that all patients develop nephritis after scarlet fever or other streptococcal infections seems to Lyttle as well as to the author unreasonable but whether the difference between this micronephritis or renal irritation and true outspoken acute glomerulonephritis is qualitative or quantitative cannot be settled at the present time The difficulty in differentiating acute glomerulonephritis and the effects of certain sulfonamide drugs upon the kidney has already been emphasized

In cases of acute glomerulonephritis in which gross hematuria persists particularly when associated with dysuria and pain in one or both costovertebral angles urologic aid may become necessary to establish the diagnosis If the amount of albumin in the urine is massive and red blood cell casts are present and if edema or hypertension is found the diagnosis is simplified In the absence of these signs it may be necessary to resort to cystoscopic examination or in

travenous pyelography to eliminate the possibilities of tumor stone tuberculosis pyelonephritis etc

The differentiation between *orthostatic albuminuria* and acute glomerulonephritis arises only in those patients who have virtually no red cells in their urinary sediments In the absence of other signs and symptoms of nephritis and in the presence of albuminuria which appears only in the erect position a diagnosis of orthostatic albuminuria becomes justifiable with repeated observations particularly when occurring in a thin child or in an adolescent

The differential diagnosis between acute and chronic glomerulonephritis is of great importance because of the difference in prognosis Nevertheless this is at times impossible particularly when an exacerbation of chronic nephritis follows an acute infection and resembles in all respects the disease in its acute form In this situation only a record of a urine examination just prior to the onset of the symptoms or the presence of signs of advanced renal disease will help to distinguish between the acute and chronic forms In the absence of these aids the diagnosis becomes dependent upon the subsequent course

In embolic acute nephritis in which there are manifestations only of albumin casts and hematuria unless diffuse glomerulonephritis supervenes the diagnosis is dependent upon the demonstration of blood stream infection by culture

Prognosis —Less than 5 per cent of patients with acute glomerulonephritis die of this disease In fatal cases death results from one or more of the following causes (1) hypertensive encephalopathy associated with convulsions (2) cardiac decompensation frequently terminating in pulmonary edema (3) uremia and (4) bronchopneumonia or sepsis

Most patients who are attacked by acute glomerulonephritis recover completely although authorities differ widely as to the actual percentage In children it is generally conceded that the prognosis is particularly good The course of the disease may last but a few days or it may persist for more than a year and yet terminate in recovery Perhaps the most frequent duration of acute nephritis among hospitalized patients is about two months It is important to recognize that the duration of acute glomerulonephritis and the ultimate outcome in terms of healing or of the development of chronic nephritis are independent of the severity of the preceding infection and the apparent severity of the disease as measured by the degree of albuminuria hematuria hypertension or edema In other words the clinical course in one patient while distinctly alarming may terminate favorably within two or three weeks whereas in another patient an apparently benign clinical course may progress to fatal chronic nephritis Although it is apparent that the ultimate outcome in acute nephritis cannot be predicted the impression has been gathered that healing is most frequent when the onset of the preceding infection is accompanied by severe constitutional reaction At this point it should be emphasized that when a patient recovers completely from acute glomerulonephritis *i e* when the urine becomes free from albumin red blood cells and casts permanent immunity for reasons unknown is almost invariably established regardless of the frequency or severity of subsequent streptococcal infections

Treatment —In the absence of specific therapy the treatment of nephritis must be largely symptomatic and in so far as possible based on recognized physiologic or biologic principles *Bed rest* is the first and most important therapeutic indication Ideally the patient should be kept in bed until all symptoms and signs of acute nephritis have disappeared Practically bed rest should be continued until all the general manifestations have disappeared In spite of the fact that small amounts of albumin and a few red blood cells may continue in evidence in the urine for six months or a year after the onset of the disease it is usually impossible to keep the patient at rest for this length of time If the urinary findings persist after two months and the extrarenal signs have vanished and if the erythrocyte sedimentation rate has returned to normal the patient may be allowed up If this change is associated with an increase in albuminuria or hematuria further bed rest is indicated Exposure to chilling and exposure to individuals with upper respiratory infection should be avoided The *dietary restrictions*

in acute glomerulonephritis depend to a large extent upon the presence or absence of oliguria edema hypertension and nitrogen retention Even in the absence of these findings the *restriction of sodium chloride* or bicarbonate is indicated as sodium salts constitute the chief 'building block of edema fluid When the course of the disease proceeds rapidly in the direction of the fulminating picture previously described limitation of food and fluids to 800 cc of fruit juices or weak tea or 25 per cent glucose solution a day may aid in preventing the rapid accumulation of fluid and the development of hypertensive encephalopathy or cardiac insufficiency This regime should not be continued for more than three or four days In milder forms of the disease a salt poor diet containing perhaps 50 to 60 Gm of protein a day seems to be the only dietary indication There is however no sound clinical evidence to suggest that the amount of protein in the diet in any way influences the course or outcome of acute glomerulonephritis

Medication—No drugs are indicated in the treatment of acute nephritis except in the presence of hypertensive encephalopathy Here the daily administration of 15 to 30 Gm of magnesium sulfate by mouth and the slow intravenous administration of 25 cc of 10 per cent olution of the same salt may have some effect in lowering the blood pressure and in preventing convulsive seizures When these measures fail the intravenous injection of hypertonic glucose solution morphine venesection and lumbar puncture are resorted to but usually without striking benefit Diuretics have no place in the treatment of acute nephritis and at times appear to add to the renal damage Therapeutic hyperthermia is distinctly dangerous in that it not infrequently contributes to cardiac insufficiency The use of diathermy over the renal area has been recommended in recent years but in the writer s experience it has been entirely without effect The *surgical treatment* of acute nephritis consists in decapsulation of the kidneys on the theory that the resulting decrease in tension permits greater blood flow Most reports suggest that the results obtained by this method in the treatment of anuria are disappointing The procedure has no justification in conditions other than "renal shut down'

In view of the intimate relation between streptococcal *infection* and the etiology of acute nephritis it is logical to eliminate all active and potential foci If sinusitis or mastoiditis is present surgical treatment should not be delayed When nephritis follows tonsillar infection these structures should be removed when the general manifestations of nephritis have disappeared In other cases tonsillectomy may be postponed until later *in convalescence Acute exacerbations of* nephritis frequently follow tonsillectomy and are usually characterized by an increase in hematuria These flare ups of the disease subside as a rule in a few days This radical point of view toward tonsillectomy is justified only by the fact that many capable observers still stress the relationship between persistent infection and the progressive nature of the nephritic process in many cases Further study may show however that this relationship is coincidental rather than causal and the writer from his experience must confess that he ha never been convinced that tonsillectomy has significantly altered the outcome of acute glomerulonephritis

In view of the close association of streptococcal infection and acute glomerulonephritis the role of *sulfonamide therapy* deserves consideration It has recently been demonstrated that sulfanilamide given in the course of acute glomerulonephritis does not increase the intensity of the nephritic process Evidence suggesting a specific effect of the drug on the disease is however not convincing Nevertheless sulfanilamide should be administered if active hemolytic streptococcal infection continues after the appearance of the nephritis Sulfapyridine sulfathiazole and sulfadiazine cannot at the present time be considered the drugs of choice because of their known effects upon the kidney

Robert F Loeb

CHRONIC GLOMERULONEPHRITIS

Clinical Picture—The clinical picture of chronic glomerulonephritis is even more variegated than is that of the acute form of the disease Only a small minority of cases

is observed to develop from an attack of typical acute glomerulonephritis following an acute infection with the hemolytic streptococcus The majority of patients with chronic glomerulonephritis seek medical aid because (1) they have noted the insidious onset of edema primarily dependent in nature (2) they complain of recurrent headaches which are usually associated with hypertension (3) they have developed dyspnea which may be exertional or paroxysmal in nature and is also as a rule related to the presence of hypertension or (4) they have been discovered on routine examination to *have albuminuria This last group* comprises about 10 per cent of a series studied at the *Presbyterian Hospital Probably* weakness lassitude and loss of weight are the commonest of all symptoms but they are characteristic of chronic disease in general and thus lose special diagnostic significance

To cases where albuminuria and cylindruria alone determine the presence of chronic glomerulonephritis the term *latent nephritis* has been applied It is reported by a number of observers that a few patients with this quiescent form of the disease recover completely Far more frequently another course is followed Either with or without persistent or recurrent infection the disease in a number of these patients becomes active as determined by an increasing number of red blood cells excreted in the urine With this *increase in activity* there may appear any or all of the symptoms and signs characteristic of outspoken acute nephritis and the patient may die with convulsions or in true uremia Autopsy in these instances shows the presence of subacute nephritis This active phase of chronic nephritis may on the other hand again become latent, only to recur repeatedly In the following months or years hypertension anemia nitrogen retention and finally the full blown picture of uremia will terminate the disease unless the course be intercepted earlier by fatal cerebral *hemorrhage or* cardiac failure Other patients enter the *nephrotic state* described fully in conjunction with the nephroses and remain water logged for months or years These patients either die of intercurrent infection *e g* bronchopneumonia or their edema subsides When the edema decreases the disease may again become latent with little or no demonstrable impairment of renal function More *frequently however*, the loss of edema presages further advance of the disease As fluid vanishes the blood pressure in time begins to rise and the development of this *hypertensive phase* is often accompanied by severe headaches and varying degrees of *cardiac insufficiency* Progressive failure in renal or cardiac function or both then terminates the disease Many patients pass directly into the hypertensive phase without ever having had more than minimal edema of the ankles or face In a few patients the advance of chronic nephritis is so gradual and so devoid of symptoms that a patient comes first to the ophthalmologist complaining of blurred vision and then in the course of a few weeks dies in uremia

The patient with chronic glomerulonephritis on inspection not infrequently presents the picture of health In the nephrotic stage striking pallor accompanies the edema and probably results in part from wide separation of skin capillaries by edematous tissues In the terminal stages of chronic nephritis the patient presents a classic appearance He looks weary and pallor now due to anemia is accompanied by a characteristic sallow tint His rest is frequently disturbed by muscle cramps The skin becomes dry and atonic and in advanced uremia in the colored race more frequently than in the white is often covered by the so-called urea frost" Mild exophthalmos commonly appears with the advance of hypertension The breath develops a typical odor wrongly termed uriniferous Fibrinous pericarditis occasionally accompanied by fibrinous pleurisy appears in about 40 per cent of patients within two weeks of death Muscular twitching occasionally due to tetany *occurs with* great regularity and when acidosis is marked hyperpnea appears Pruritus leads to uncontrolled scratching by the stuporous patient Bleeding from the nose or gastrointestinal tract is a common terminal manifestation In addition to dyspnea and Cheyne Stokes breathing probably the most distressing subjective symptoms are those of complete gastric intolerance coupled with thirst Most patients die in coma but fifteen of fifty seven patients at the Presbyterian Hospital who died of this disease and were examined postmortem had had terminal gen

eralized convulsions and in nine pulmonary edema was present

The frequency with which *edema* appears in chronic glomerulonephritis is indicated by the fact that among sixty seven patients who died of the disease at the Presbyterian Hospital this manifestation was recorded at some time in the records of fifty seven It was mentioned as being facial in twenty seven instances and dependent in forty nine The edema which appears during acute ex acerbations is probably caused by the fac tors mentioned in the discussion of acute nephritis In the nephrotic phase the most important factor is a decrease in the albumin fraction of the serum proteins The reader is referred to the section on nephrosis for further information

In all of fifty seven patients with chronic glomerulonephritis examined postmortem at the Presbyterian Hospital *hypertension* was present On the other hand in the so called latent phase of the disease the blood pres sure may remain normal for many years For example in a patient seen in the Presby terian Hospital with edema hypertension nitrogen retention albuminuria and hem aturia the blood pressure now twenty two years later is normal and only albuminuria and cylindruria persist In another patient refused a position because of albuminuria fifteen years ago the blood pressure is nor mal despite the facts that edema and head ache required hospitalization eleven years ago and that the patient has had many subsequent respiratory infections due to the hemolytic streptococcus Thus it is apparent that hypertension while it may occur early in the disease at which time it fluctuates considerably is a relatively constant finding only as chronic nephritis progresses to its termination The height of the level attained is variable but involves both the systolic and *diastolic pressures In thirty nine of a* group of fifty-seven studied postmortem the systolic pressure was above 190 mm mer cury and in sixteen of the group it reached levels higher than 230 mm mercury

Disorders of the *heart* appear late in the course of chronic nephritis and are associ ated with the presence of hypertension In a patient in whom the disease progresses rapidly hypertension and cardiac insuf ficiency may develop within a few months after the apparent onset of the disease On the other hand chronic glomerulonephritis may be present for many years before any elevation of blood pressure or impairment of cardiac function takes place Cardiac hyper trophy and dilatation may develop slowly or rapidly after the appearance of hyper tension but neither the degree of cardiac embarrassment nor the size of the heart can be directly correlated with the height of the arterial pressure or with its duration Hence it is fair to suspect that factors other than work contribute to cardiac hypertrophy in chronic nephritis

In the series of patients studied post mortem at the Presbyterian Hospital more than 90 per cent complained of dyspnea This was usually exertional in nature but about 20 per cent of the patients also com plained of paroxysmal dyspnea and had terminal pulmonary edema In a number of patients even in the absence of frank signs of left ventricular insufficiency there may be elevation of the venous pressure which contributes to edema In the uremic state gallop rhythms are frequently heard and as has been stated above about 40 per cent of the patients have a sterile fibrinous or serofibrinous pericarditis There are no char acteristic electrocardiographic changes asso ciated with the cardiac insufficiency of chronic nephritis but left ventricular pre-ponderance naturally appears at times The heart at postmortem weighed more than 400 Gm in 70 per cent of the Presbyterian Hospital cases thus corresponding to the enlargement found on x ray examination

The *cerebral* manifestations in chronic nephritis should be considered primarily in conjunction with hypertension Many pa tients without edema or hypertension com plain of headache and in view of its fre-quency without renal disease it seems likely *that it is often falsely attributed to neph* ritis About 30 per cent of patients with chronic glomerulonephritis are entirely free from headache while in the remainder it may be mild and infrequent even though hypertension be present On the other hand almost daily headaches torture some pa tients for long periods of time they may occur at any time of day and are accentu ated by fatigue Sometimes pain is present on awakening in the morning and disappears

a few hours later The mechanism of this distressing symptom is not understood particularly as it comes and goes without necessarily being associated with any change in arterial tension Classic hypertensive encephalopathy culminating in convulsions is rare and usually fatal in chronic nephritis The epileptiform seizures seen in the terminal stages of the disease are probably related to renal failure with the retention of substances leading to increased irritability of the nervous system

The majority of patients with chronic glomerulonephritis complain of some *visual disturbance* late in the disease This is usually characterized by blurring of vision and less frequently by blindness Ophthalmoscopic examination reveals arteriolar changes in most patients in whom hypertension has been established for some time Edema of the optic disks or the retinae appears in more than half the patients and exudate and hemorrhage have approximately the same incidence These changes in the fundi may occur singly for years and may vary in degree from time to time, but when all the changes enumerated are present the duration of life is as a rule less than two years

The *blood* in chronic glomerulonephritis may remain normal for many years but anemia finally develops in most patients Thus in the Presbyterian Hospital series the red blood count was less than 3 000 000 per cubic millimeter in about 60 per cent of the patients in advanced stages of the disease The color index varied between 0 8 and 1 2 in 70 per cent In other cases perhaps associated with bleeding the anemia is definitely hypochromic while very occasionally it is hyperchromic in type Isaacs has found that the bone marrow in chronic nephritis shows that there is a tendency for hematopoiesis to be arrested in the erythroblastic stage The development of anemia is usually gradual and yet the writer has seen the hemoglobin fall more than 30 per cent in twelve days without hemorrhage without increase in bilirubinemia without increase in reticulocytes and in the face of repeated transfusions The white blood cells show no particular change from normal The hemorrhagic diathesis seen in uremia results from an increase in capillary fragility Bleeding from the nose or gastro intestinal tract or purpura develops terminally in about two thirds of the patients The changes in the serum proteins and lipoids in the nephrotic phase of glomerulonephritis are described elsewhere, inasmuch as they are qualitatively and quantitatively the same as in true nephrosis In advanced glomerulonephritis the serum proteins may be normal or decreased in amount

The *urine* in chronic nephritis varies in its characteristics depending upon the degree of activity of the disease In the latent phase, albuminuria may be minimal or marked and cylindruria is variable and by arbitrary definition red blood cells in the urinary sediment if present at all are few in number When the nephritis is active red blood cells are numerous and the urine has the characteristics of that seen in acute nephritis it may be smoky in appearance or even grossly bloody Microscopic hematuria may be recurrent and transient in nature or it may persist over a period of years In general cases in which red blood cells persist in large numbers run a relatively rapid course However the writer has seen one patient who under almost constant observation showed persistent and marked microscopic and at times macroscopic hematuria for twelve years before she succumbed to her disease In the nephrotic phase of chronic nephritis the urine contains large amounts of albumin whereas red cells while frequently numerous are at times present in only small numbers thus making it difficult in the latter case to distinguish it from true nephrosis As nephritis progresses and usually when the kidneys have become reduced in size through extensive fibrosis the specific gravity becomes fixed between 1 008 and 1 012 In this advanced stage albuminuria cylindruria and microscopic hematuria frequently decrease strikingly The late changes in renal function receive their physiologic explanation through the fact that few glomerular units are capable of function and tubular degeneration prevents normal reabsorption and secretion

As the ability of the kidneys to concentrate gradually diminishes the patient compensates for this physiologic defect by increased thirst and increased ingestion of fluid *Nocturia* i e nocturnal polyuria ensues and occasionally constitutes the pre-

senting symptom in patients whose disease has progressed silently to an advanced degree

Renal function may decrease rapidly and a patient may die in uremia in the course of a few months following the onset of the disease On the other hand in many cases of chronic glomerulonephritis there may be normal renal function for many years as measured by the usual tests Thus the ability to concentrate is gradually impaired and the urea clearance decreases as does the excretion of phenolsulfonphthalein or other dyes As impairment of function advances particularly if the fluid intake of the patient be restricted accumulation of the end products of nitrogen metabolism gradually takes place over a period of many months In other patients the specific gravity of the urine may remain fixed for months or years without associated nitrogen retention and then either with or without the development of cardiac insufficiency or in the presence of infection or after an operation renal decompensation may occur rapidly and the patient dies in uremia in the course of a few weeks In exceptional cases severe renal decompensation as indicated by nitrogen retention may be present for years For example the author had a patient who after six years of active glomerulonephritis proved postmortem reached a point where her excretion of phenolsulfonphthalein in two hours was nil her blood urea was 90 mg per 100 cc and her creatinine was 6 mg per 100 cc She worked most of the time during the next six years and annual observations showed persistence of her markedly impaired renal function with further accumulation of urea in the blood Late in her disease she had also an acidosis which is common terminally These cases of prolonged renal insufficiency when they occur early in childhood produce *dwarfism* associated with osteoporosis and are inappropriately described as *renal rickets* The nature of the chemical disturbances occurring in advanced nephritis is discussed in the section on uremia

Diagnosis —The diagnosis of chronic glomerulonephritis is usually simple and is based on the continued presence of albuminuria cylindruria and varying degrees of microscopic hematuria either with or without extrarenal manifestations of the disease Under a number of circumstances however the diagnosis is difficult and yet it is important from a practical standpoint as prognosis and therapeutic indications may depend upon it It has already been pointed out that the differential diagnosis between acute nephritis and an exacerbation of chronic nephritis is at times impossible Nevertheless marked enlargement of the heart extreme degrees of hypertension thickened and tortuous arteries changes in the eyegrounds severe anemia marked lowering of the serum proteins and fixations of the specific gravity of the urine point definitely to a chronic process although they do not in rare instances preclude the possibility of the acute form with a subsequent favorable outcome The differentiation of the nephrotic phase of chronic glomerulonephritis and true nephrosis is also difficult In both of these depression of the basal metabolic rate lipemia hypoproteinemia with inversion of the albumin globulin ratio and heavy albuminuria occur Marked elevation of the blood pressure enlargement of the heart gross or marked microscopic hematuria and changes in the eyegrounds make chronic glomerulonephritis the more likely diagnosis The age of the patient also lends some significance as true nephrosis among adults is extremely rare That even these criteria at times fail is apparent from the fact that among the writer s patients was a boy of fifteen who was proved at autopsy to have pure nephrosis despite the elevation of blood urea to 100 mg per 100 cc the fact that his blood pressure reached a level of 160/100 and that occasional red cells were present in the urinary sediment The differentiation between orthostatic albuminuria and nephritis has been discussed in conjunction with acute nephritis

In all patients presenting the picture of advanced renal insufficiency the possibility of renal disease other than nephritis must be borne in mind Bilateral pyelonephritis with or without stones bilateral renal tuberculosis hydronephrosis due to ureteral or prostatic obstruction and advanced polycystic disease of the kidneys may all terminate in uremia Hence when confronted with advanced renal disease in which the etiology is not certain it is often impossible to characterize the renal lesion without

knowledge of the natural history of the dis ease and the application of the appropriate urologic techniques

Prognosis—The prognosis in chronic glomerulonephritis is ultimately bad but the speed with which the disease reaches its fatal termination is extremely variable It is practically impossible to estimate the probable life span of a patient on the basis of a single set of clinical observations and tests of renal function and it is not infrequently difficult to estimate it even with the aid of repeated observations over a period of months or years For example a patient may be seen in an acute exacerbation of the disease and then may enter the latent phase and lead a normal and useful existence for many years before his disease reaches the uremic state On the other hand another patient may have nephritis of apparently identical severity and yet his disease may progress to its termination in a few weeks or months Despite these discouraging comments there are features of the disease which distinctly facilitate prognosis When the disease is ac companied by persistent and marked micro scopic hematuria it usually ends fatally in months or at best in a few years If the dis ease is accompanied by progressive elevation of the blood pressure the outlook for more than a few years is poor When progressive cardiac insufficiency develops a return to a more benign course is distinctly unusual The presence of choked disks arterial changes hemorrhages and exudate in the eyegrounds offers as a rule a prognosis of less than two years The progressive devel opment of anemia likewise indicates that an advanced stage of the disease has been reached Pericarditis when it occurs devel ops terminally Single tests of renal function except relatively late in the course of chronic glomerulonephritis offer little of prognostic value but repeated observations made in the course of the disease may reveal a curve indicating the velocity of its progression When the urea clearance is reduced to minimal values when the excretion of phenolsulfonphthalein is virtually zero and nitrogen retention increases progressively the prog nosis can usually be measured in months instead of years It must be recognized how ever that there are exceptions to the general statements as is shown by the writer s patient who was able to continue work for six years after her excretion of phenolsulfon phthalein and the level of blood urea and creatinine suggested a prompt demise An other patient whose blood urea was 500 mg per cent and who had profound anemia left the hospital after treatment with trans fusions and infusions and worked for eight months before death occurred

Treatment—In the latent stage of chronic nephritis there are no therapeutic indications other than warning the patient against overfatigue and ridding him of ob vious foci of infection particularly in the upper respiratory tract Certainly dietary restriction is not indicated when the only pathologic manifestations consist of albu minuria and cylindruria Patients in this phase of the disease should be instructed to seek medical aid if symptoms or signs de velop and they should be seen by their phys ician routinely at perhaps yearly intervals in order to have the status of their disease appraised This annual survey should in clude examination of the urine a blood count blood urea and serum protein deter minations as well as a physical examination with emphasis laid on the heart blood pres sure eyegrounds and presence of edema Abnormalities found in the course of these studies may necessitate the instigation of active therapeutic measures If activity develops as determined by hematuria par ticularly if associated with edema and hypertension bed rest is indicated and the treatment is that of acute nephritis The patient should be urged to remain in bed at least until the generalized signs have dis appeared and if possible until microscopic hematuria becomes minimal

In the nephrotic phase also bed rest is indicated as this tends to inhibit the devel opment of edema It is in this phase of chronic glomerulonephritis that the most definite indication for dietary regulation is encountered Rigid salt restriction and the incorporation of enough protein in the diet to maintain nitrogen equilibrium constitute the basic principles involved The custom of forcing the protein intake beyond the body requirements in the writer s experience has failed to attain its theoretical end namely that of raising the serum protein level Addis believes that it is of vital importance to

keep the protein of the diet at the lowest possible level compatible with nitrogen equilibrium In the opinion of the writer the evidence presented does not warrant this rigid restriction of protein Details of this aspect of therapy are discussed in conjunction with the nephroses Patients in the nephrotic state are especially susceptible to infection of the respiratory tract and should be protected from exposure

The symptomatology associated with hypertension is particularly distressing to patients The *headaches* sleeplessness nervousness and irritability are trying Sedatives particularly chloral hydrate and bromide in small doses are useful in the treatment of these symptoms Daily periods of rest and the avoidance of unnecessary physical exertion which may add further cardiac strain are also of great importance as is the prevention of obesity through dietary restriction Regulation of the bowels and even free catharsis in addition to the use of analgesics should be resorted to in the treatment of hypertensive headaches The treatment of hypertensive encephalopathy has been discussed in the section on acute nephritis

Cardiac insufficiency whether incipient or outspoken demands bed rest and the principles involved in its treatment are those which apply to cardiac decompensation in general The problem of fluid regulation is difficult because rigid limitation is indicated in congestive heart failure whereas with renal insufficiency enhanced by the inability to concentrate the liberal ingestion of fluid should be maintained to curb nitrogen retention In such a situation the treatment of the cardiac insufficiency deserves first consideration and moderate restriction of fluid perhaps to 1500 cc a day may be tried Salt restriction and a cardiac diet with an allowance of about 50 Gm of protein a day should be employed Digitalis and sedatives are indicated as in other congestive disorders of the heart In the presence of an elevated venous pressure and especially when associated with pulmonary edema phlebotomy may afford relief This procedure naturally has no place when anemia is present The use of diuretics particularly the mercurials is contraindicated in the presence of renal insufficiency as these substances not infrequently induce hematuria or anuria While cardiac insufficiency causes some depression of the excretion of phenolsulfonphthalein as well as of urea its effect on renal function is not extreme For example if the phthalein' excretion in two hours is less than 30 per cent and if the blood urea is higher than about 75 mg per 100 cc it is probable that nephritis is present in addition to congestive heart failure In these cases of cardiac decompensation where the integrity of the kidney is in doubt the employment of diuretics should be undertaken only with extreme caution

The treatment of the *anemia* of chronic nephritis is both important and difficult Profound anemia contributes to weakness cardiac insufficiency edema and probably to the degree of renal failure The effects of large doses of iron and of liver extract are notoriously disappointing as might be anticipated from the fact that the anemia is essentially aplastic in type Where the anemia is hypochromic perhaps due to hemorrhage some benefit may be expected from iron therapy Transfusions offer the best results but these should be given slowly If hypertension or cardiac insufficiency be present it is desirable to have venous pressure determinations made during transfusions in order that pulmonary edema may be avoided

Pregnancy as a rule and for reasons unknown intensifies chronic glomerulonephritis If pregnancy is not interrupted many patients either abort or develop a toxemia after the fifth month On the other hand a certain number of women are able to reach term and are delivered of healthy babies despite the presence of chronic glomerulonephritis In deciding whether or not pregnancy should be terminated each case should be considered individually If the patient s desire to continue pregnancy is great her request should be granted with the understanding that premature labor may have to be induced promptly if the blood pressure rises edema increases or other signs of toxemia begin to appear

The problems concerned with the management of advanced nephritis are discussed in the section on uremia

ROBERT F LOEB

ARTERIOLAR NEPHROSCLEROSIS

Hypertensive vascular disease terminates in cerebral hemorrhage cardiac insufficiency or uremia In this section we are concerned with that 10 per cent of patients whose disease leads to renal insufficiency The term 'arteriolar nephrosclerosis is applied to involvement of the renal area by hypertensive vascular disease giving rise to disturbances in renal function associated with the development of a clinical picture identical with chronic glomerulonephritis

Etiology and Mechanism —The etiology and mechanism of hypertensive vascular disease are unknown Consequently it is not surprising to find innumerable theories concerning this subject Thus the endocrine glands have been implicated because hypertension constitutes an important part of the clinical picture in the Cushing syndrome due to basophilic adenoma of the pituitary gland as well as in certain cases of tumor of the adrenal glands Pressor substances derived from kidneys rendered ischemic by means of Goldblatt clamps have been isolated in the dog by Braun Menendez and by Page The importance of the elaboration of hypertensin from renin in human hypertensive disease has, however not been definitely established Reflexes associated with mechanical obstruction of the cerebral and renal circulations have also been considered as initiating factors in the disease Direct toxic action of unknown substances derived from unknown sources has been assumed to injure the arterioles and hypertension has been considered secondary to these changes The importance of any or all of these factors in the development of the clinical and histologic picture of hypertensive vascular disease either with or without involvement of the renal area is still obscure

It is probable that the clinical pattern seen in arteriolar nephrosclerosis represents a syndrome rather than a disease entity because of the diverse nature of disorders with which it may be associated For example in one instance it represents the aftermath of pyelonephritis in childhood in another it may develop with lead intoxication in still another it may appear in the course of chronic glomerulonephritis or secondary to pregnancy In the majority of cases it begins insidiously and apparently as a vasospastic phenomenon without a recognized relation to other disease processes

Predisposing Factors —*Arteriolar* nephrosclerosis occurs most frequently in middle age, although it may occur at any age after the first decade When it develops in the second and third decades it is more apt to be acute in its nature and to run a fulminating course The distribution among the sexes shows a slight preponderance among females perhaps because pregnancy frequently appears to play a role in the disease Lead and arsenic poisoning and pyelonephritis are at times either predisposing or inciting factors There is a strong familial tendency toward hypertensive vascular disease and the so called "sthenic type' appears to be particularly susceptible

Pathology —Two general types of lesions are encountered in the kidneys in nephrosclerosis The differences in these types are related to the velocity with which the disease has progressed to its termination, but whether they are due solely to the speed of the morbid process or whether two different mechanisms are involved is not known When the progression of hypertensive vascular disease is slow and the patient dies of renal insufficiency after many years the term benign nephrosclerosis is employed in contradistinction to malignant nephrosclerosis In the latter form the patient succumbs in a few months or perhaps in a year or two In dogs Goldblatt has been able to produce the exact prototype of benign and "malignant' hypertensive disease by applying lesser or greater constriction to the renal arteries by means of special clamps

Postmortem the kidneys from a patient with slowly progressive arteriolar nephrosclerosis are usually smaller than normal the surface is roughly granular brownish red in color and adherent to the capsule On section the cortex is irregularly narrowed Histologic examination reveals extensive thickening of the arterioles with narrowing of their lumina The intima shows marked widening and there is reduplication of the elastic lamellae The glomeruli may show striking changes The basement membrane

of the tufts is first thickened and the glomeruli are frequently ischemic In other glomeruli the tufts are hyalinized and the parietal epithelium becomes markedly thickened by fibrous tissue The *tubules* degenerate and in time tubular elements may become cystic or entirely disappear The *interstitium* shows marked fibrosis From this brief description of the histologic changes in the so-called benign form of arteriolar nephrosclerosis it may be seen that the picture closely resembles that present in advanced glomerulonephritis As a matter of fact it is frequently impossible to state on the basis of gross or microscopic study whether the glomerular changes are secondary to arteriolar lesions or whether the reverse is true

In cases of arteriolar nephrosclerosis which have run a rapid course (the so called malignant type) the changes described above are present in varying degrees and superimposed are those thought to be characteristic of the malignant form The kidneys in these cases may be contracted or they may be normal in size or even slightly enlarged The surface is more or less granular and hemorrhages are common The cortex is usually narrowed to varying degrees Microscopic examination reveals the changes already mentioned in the arterioles but in addition necrosis and endarteritis are present Rupture of degenerated arterioles is not uncommon The glomeruli show cellular proliferation as well as swelling and droplet formation The tubules show varying degrees of degeneration and the lumina may be filled with cellular detritus and blood These changes in the tubules and glomeruli are also seen in chronic glomerulonephritis although in the latter disease they are usually more diffuse

Clinical Picture.—The clinical picture of arteriolar nephrosclerosis is dominated by the various manifestations of hypertension For months or years depending upon the rate of evolution of the disease the urine shows no abnormalities Then if cardiac or cerebral complications do not first terminate the disease albuminuria and cylindruria of varying degrees appear In this stage hypertension alone with the symptoms and signs attending it serves to distinguish the disease from glomerulonephritis in the latent phase If the progress of arteriolar nephrosclerosis is rapid the picture of rapidly advancing nephritis appears within a few months If the disease is of the 'benign type renal function may not be compromised for many years despite the persistence of albuminuria Sooner or later however the clinical picture seen in advanced glomerulonephritis makes its appearance Observations made early in the course of the disease may give the only clue as to whether a patient with advanced nephritis is suffering from arteriolar nephrosclerosis or from chronic glomerulonephritis For example if hypertension is known to have been present before the appearance of albuminuria the diagnosis of nephrosclerosis is obvious whereas in chronic glomerulonephritis albuminuria precedes the development of hyper tension The nephrotic syndrome with marked depression of serum proteins and inversion of the albumin globulin ratio also serves as a distinguishing feature since it does not occur in arteriolar nephrosclerosis *e g* the serum protein concentration was found to be greater than 5 per cent in sixteen of seventeen patients dying of the disease at the Presbyterian Hospital *Edema* occurs in about 70 per cent of patients with nephrosclerosis and is due either to associated cardiac insufficiency or to the fact that the remaining glomeruli are incapable of function adequate to maintain water balance

It is often stated that the presence of *hematuria* either gross of microscopic is much more characteristic of glomerulonephritis than of nephrosclerosis but of forty six patients dying of the latter condition three had gross hematuria and red cells were found microscopically in the urine of thirty two It can be shown statistically that the *degree of hypertension* tends to be greater in nephrosclerosis than in chronic glomerulonephritis In the Presbyterian Hospital series of patients with nephrosclerosis examined postmortem twenty six of thirty seven patients had a systolic pressure above 230 mm mercury Thus the incidence of hypertension of this order of magnitude is greater in this group than in the corresponding group with chronic glomerulonephritis However in an individual patient the blood pressure level can have no differential diag

nostic significance The blood pressure shows wide fluctuations depending upon the mental state and the amount of physical activity, but, as the disease progresses, the favorable effect of rest becomes less apparent *Cardiac hypertrophy* occurs with great regularity in arteriolar nephrosclerosis and tends to be slightly greater in degree than in chronic glomerulonephritis *Dyspnea* and *congestive heart failure* with or without pulmonary edema are equally common in both diseases *Headache* as might be anticipated is one of the commonest complaints and was present in 80 per cent of the series studied postmortem at the Presbyterian Hospital It varies in intensity as is true in glomerulonephritis The *eyegrounds* showed definite arterial changes in over 90 per cent of the Presbyterian Hospital series Exudate hemorrhages and papilledema were each present at some time in about 70 per cent of the patients dying of arteriolar nephrosclerosis Many statements in the literature suggest that the retinopathy of arteriolar nephrosclerosis may be differentiated with great regularity from the changes present in chronic glomerulonephritis with hypertension but in the experience of the writer this is not the case The *anemia* associated with advanced nephrosclerosis may be of the same severity and type as that present in glomerulonephritis although it appears to occur a little less frequently Disturbances in *renal function* are naturally dependent upon the extent of the arteriolar nephrosclerotic process, but when the disease progresses to an advanced stage the loss of the ability to concentrate the depression of urea clearance and excretion of phenolsulfonphthalein and the retention of the end products of nitrogen metabolism occur just as in late glomerulonephritis

Diagnosis—The diagnosis of arteriolar nephrosclerosis is suggested by the development of hypertension with the subsequent appearance of albuminuria and cylindruria terminating in uremia The difficulties both clinical and pathologic encountered in differentiating this disease from chronic glomerulonephritis have been discussed They are of only academic importance as the prognosis and therapy of both disorders are essentially the same when that stage is reached in which identical physiologic disturbances are present

It should be kept in mind that arteriolar nephrosclerosis may be associated with lead poisoning Theoretically one might expect improvement in the vascular disease with the treatment of saturnism, but practically no alleviation has been noted Arteriolar nephrosclerosis may result from pyelonephritis and when this is suspected urologic studies may clarify the diagnosis Unfortunately when the stage of arteriolar nephrosclerosis has been reached the mechanism of its production alters neither therapy nor prognosis The variation in the velocity of its course has already been discussed in connection with the terms benign and "malignant' forms

Prognosis—Patients suffering from arteriolar nephrosclerosis die eventually of uremia unless cardiac insufficiency or cerebral hemorrhage terminates the disease It has been pointed out that the disease may be rapidly progressive, running its course in a few months or it may progress gradually over a period of many years In a number of cases the disease may change its nature abruptly the slow progress of the so called benign form becoming accelerated and the rapid downhill course of the so called malignant type then leading to uremia in the course of some weeks

As is also true of glomerulonephritis no prognosis can be given on the basis of a single series of observations unless the picture of advanced nephritis is present In the absence of demonstrable renal insufficiency, it is frequently impossible to prognosticate the course of arteriolar nephrosclerosis even with observations extending over some years The height of the blood pressure is occasionally ascribed to have prognostic significance but the rate of progression of renal insufficiency can in no way be correlated with the degree of hypertension For example the writer had a patient whose blood pressure at thirty three years was 268/160 Her eyegrounds at this time showed arteriolar changes and her urine contained a little albumin This patient was seen regularly over a period of twelve years after which time her blood pressure was still above 250 mm mercury Her urine continued to show only a very faint trace of albumin her blood

urea was normal and at autopsy (death resulting from cerebral hemorrhage) only moderate nephrosclerosis was present

Treatment —In the absence of any specific therapy the medical treatment of nephrosclerosis resolves itself into the management of hypertension and of chronic nephritis both of which are discussed elsewhere in this volume

In recent years a variety of surgical measures has been introduced in the treatment of hypertensive vascular disease The most promising of these consists in the resection of the splanchnic nerves How much permanent relief may be afforded by this method of treatment and how much it may influence the progression of arteriolar nephrosclerosis cannot be stated at this time Nevertheless in selected cases this approach to therapy appears to offer the patient more than does the alternative laissez faire attitude

ROBERT F LOEB

MISCELLANEOUS NEPHRITIDES

Acute Interstitial Nephritis —This constitutes an anatomic rather than a clinical entity and is characterized by a diffuse infiltration of the renal interstitium with red blood cells polymorphonuclear cells and lymphocytes Edema of the tissues may be present also There are no characteristic glomerular or tubular lesions This disorder of the kidneys is usually associated with severe sepsis or with diphtheria and constitutes a postmortem finding without known clinical significance

Transfusion Nephritis —This type of nephropathy (not nephritis) usually follows transfusion from a donor whose blood is incompatible with that of the recipient although occasionally no incompatibility can be demonstrated by the usual methods of blood grouping There is usually a chill after transfusion The patient then may have hemoglobinemia or hematuria and jaundice may appear In the next twenty four to forty eight hours oliguria complete anuria and edema make their appearance The classic picture of uremia develops and may end fatally in ten to twenty days A number of patients recover spontaneously even though almost complete anuria persists for ten to twelve days Anatomic examination reveals that the kidneys are swollen Histologically the capsular spaces and more particularly the tubules are found to be filled with precipitated hemoglobin The glomerular tufts are often ischemic and the interstitium is edematous Large amounts of alkali given by mouth before anuria develops may inhibit the precipitation of hematin in the tubules Other therapeutic measures are palliative

Focal Nephritis —Probably most cases of so called focal nephritis (characterized by albuminuria cylindruria and microscopic hematuria without extrarenal signs and symptoms) are either true glomerulonephritis as has been intimated elsewhere or they are embolic in nature appearing in the course of infection In other cases probably nephritis is not present at all and the albuminuria cylindruria and microscopic hematuria merely represent the result of increased capillary porosity occurring in febrile disease

Syphilitic Nephritis —Recently Rich has described a characteristic histopathologic picture in the kidneys of a number of patients with tertiary syphilis These changes consist in a diffuse infiltration of the interstitium with lymphocytes macrophages and plasma cells The process characteristically shows encroachment of these cell accumulations upon the tubules in which there may be deposits of cholesterol crystals In later stages scarring of the interstitium atrophy of tubules and hyalinization of glomeruli take place The clinical picture in these cases is indistinguishable from certain cases of chronic glomerulonephritis or from cases of arteriolar nephrosclerosis If the etiology of an existing nephritis could be established as syphilitic active specific therapy might alter the course of the disease In patients presenting the clinical picture of arteriolar nephrosclerosis combined with syphilis iodide therapy and small doses of arsphenamine may be administered cautiously with the patient under constant observation If microscopic hematuria or albuminuria increases or if edema or nitrogen retention appears treatment should be discontinued

Arteriosclerotic Nephritis —Arteriosclerosis of the larger branches of the renal

artery at times gives rise to areas of fibrosis in the renal parenchyma characterized on gross examination by large depressed scars It is extremely rare to find the functioning renal tissue reduced by this degenerative process *per se* to the point of serious renal insufficiency even though the kidney reserve may be definitely compromised

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THE NEPHROSES

The term 'nephrosis' was suggested in 1905 by Friedrich Mueller to designate such degenerative lesions in the kidney as could not properly be called nephritic *i e* inflammatory Since he did not include the degenerative vascular lesions, the word nephrosis came to imply disease of the renal tubules With this purely histologic connotation numerous clinical conditions known to cause such tubular damage have been classified as types of nephrosis In clinical circles however the purely morphologic approach has fallen into disuse and a more physiologic concept has taken its place The nephrotic syndrome rather than tubular degeneration of the kidneys is now the common denominator in classifying the nephroses This would seem to be an appropriate development, for the life history of mercurial poisoning for example bears no resemblance to that of true nephrosis and whereas the etiology of the former is clear that of the latter is wholly unknown There is little to be gained, therefore by grouping them together in a textbook of medicine under a single diagnostic term

If the presence of the nephrotic syndrome be accepted as the essential criterion, the nephroses include (1) *true or lipoid nephrosis* (2) *the nephrotic stage of chronic glomerulonephritis* (3) *amyloidosis of the kidney* (4) *syphilitic nephrosis* The nephrotic stage of glomerulonephritis has been discussed in relation to that disease Syphilitic nephrosis occurs during the secondary and tertiary stages of the infection and in recent years has been extremely rare at the Presbyterian Hospital in New York City This may be due to the widespread recognition of early syphilis and its adequate therapy Further mention of this entity will be found in the section on syphilis Amyloid disease also is discussed elsewhere

The Nephrotic Syndrome—The nephrotic syndrome may be defined as a clinical state characterized by the presence of edema albuminuria and decreased serum albumin There is usually in addition, an elevation in the blood cholesterol concentration and not infrequently a lowered basal metabolic rate This picture as outlined above is seen chiefly in amyloidosis of the kidneys during a stage of chronic glomerulonephritis and in true or lipoid nephrosis These conditions are grouped together because of their correlation to a common physiologic mechanism *viz* the Starling hypothesis rather than on the basis of a similarity in the histopathology of the renal tubules The first clinical application of the Starling hypothesis as an explanation of the formation of edema in nephrosis was made by Epstein in 1917 He pointed out that a low serum protein implied a lowered plasma osmotic pressure and that thereby the equilibrium between capillary blood pressure and plasma osmotic pressure at the capillary wall was altered in a direction that would further the collection of fluid in the tissue spaces It was subsequently proved by many workers that this decrease in serum protein is relatively greater in the albumin than in the globulin fraction Since the albumin molecule is much smaller than the globulin molecule it exerts a proportionally higher osmotic pressure consequently its loss from the blood stream will cause an even more serious diminution in plasma

osmotic pressure than was originally suspected There can be no doubt that this lowered osmotic pressure plays an important role in the production of edema in the nephrotic syndrome Although the validity of this mechanism in the nephrotic syndrome is unquestioned there are other factors that play a role factors less clearly appraised chief of which is the state of the capillary wall While the evidences of widespread capillary change seen in acute glomerulonephritis are not usually observed in the nephrotic group there are changes in the fluid equilibria in nephrosis which are unaccompanied by parallel changes in the osmotic pressure (protein per cent) of the plasma and for which alteration of the capillary wall would by exclusion seem to be the probable determinant

It has become increasingly apparent that the serum proteins are qualitatively altered in the nephrotic state Several analytic approaches have contributed evidence in support of this thesis Among the methods applied are electrophoretic studies precipitin reactions to specific immune sera and quantification of amino acid content particularly cystine It has not yet been demonstrated that the intrinsic composition of their serum proteins can serve to differentiate the various nephroses

Long before the importance of changes in plasma osmotic pressure was emphasized the influence of sodium chloride ingestion upon fluid exchange had been noted For years the chloride ion was assigned the chief role in the production of edema Blum showed later that whereas sodium chloride led to an increase in edema potassium ammonium or calcium chloride exerted the opposite effect sodium bicarbonate acted similarly to sodium chloride These observations pointed to sodium as the more significant electrolyte and modern work has amply confirmed Blum s investigations The present concept of the relationship of sodium to the accumulation of edema is based on the assumption that no extracellular fluid can exist in the tissues without a skeletal framework of sodium Edema fluid cannot be pure water Hence if a tendency to edema is present (due for example to a decreased serum *albumin*) restriction of sodium will tend to inhibit the production of edema On the other hand easy availability of sodium will accelerate the process other things remaining equal Thus it is obvious that the well known palliative effect of salt restriction on individuals suffering from the nephrotic type of edema has no peculiar specificity but is a benefit indigenous to salt restriction in any form of edema that is not dependent upon seepage through an altered capillary wall

The nephrotic syndrome regardless of its fundamental clinical cause has two important therapeutic approaches sodium restriction and dietary protection of the plasma protein concentration The latter may be accomplished by appropriate investigation of the food habits of the patient and the addition of adequate amounts of protein containing foods when necessary There is little evidence however to indicate that protein ingestion when forced to abnormal levels produces a significant increase in the protein content of the plasma Indeed, it is possible to induce a positive nitrogen equilibrium over long periods of time without any change in the serum protein Furthermore in spite of the consistently low concentration of amino acids in the blood of these patients parenteral administration of amino acids in adequate amounts does not influence the level of serum albumin In striking contrast to the futility of high protein diets in the nephrotic syndrome is the quick response to a normal diet when the low serum protein level is due to malnutrition

Physicians have for some years limited the intake of sodium chloride in edema The value of such therapy is no longer debatable but it is well to remind the reader that thorough sodium restriction includes not only the omission of salt in cooking but also the avoidance of sodium bicarbonate in all forms, both dietary and medicinal

DANA W ATCHLEY

TRUE OR LIPOID NEPHROSIS

Definition and Incidence—True nephrosis is a chronic disease of variable duration in which the nephrotic syndrome exists without evidence of glomerulonephritis or amyloid disease Although some writers have

denied that there is such a separate entity asserting that careful histologic search will demonstrate glomerular damage, an increasing volume of opinion is sustaining the opposite point of view The good prognosis the peculiar susceptibility to pneumococcus infections the higher incidence in children and the entire lack of renal histopathology early in the course are characteristics not to be found in other examples of the nephrotic syndrome It is only fair to add however that satisfactory differential diagnosis may require many months of observation

Nephrosis is a rare disease in adults During thirteen years of an active special clinic for the study of renal disease only three or four cases were discovered On the other hand the pediatrician finds that while it is not a common disease in children it is in no sense a rare one There is no known sex predominance nor have any facts as to racial or geographic distribution entered the literature

Etiology and Pathogenesis—The relationship to infection seen in glomerulonephritis and amyloidosis does not appear to exist in true nephrosis and indeed no convincing etiologic hypothesis has ever been propounded Moreover, no unifying mechanism capable of explaining all the characteristic features is apparent in these cases As has been stated the decrease in plasma osmotic pressure is one of the forces tending to produce edema and the hypothesis that this depletion of plasma albumin is dependent upon its loss as albumin in the urine has been widely accepted The numerous suggestions in explanation of the albuminuria need not be detailed but it should be pointed out that the urine can contain albumin in nephrosis with no determinable histologic abnormality in the kidney While there is a gross statistical correlation between serum protein levels and daily output of urinary albumin closer analysis of individual cases leads to real doubt as to the probability that this is the only factor tending to decrease serum albumin in nephrosis The failure noted above of individuals suffering from nephrosis to rebuild serum albumin in the presence of a positive nitrogen balance is further proof that the albuminuria alone cannot explain the blood changes

The high blood cholesterol and the presence of lipoid deposits in the kidney have caused some writers to suggest that true nephrosis is the result of an obscure disturbance in lipoid metabolism This has led them to designate it as "lipoid nephrosis" An hypothesis that would satisfactorily elucidate the mechanism of such pathogenesis has not been advanced

Pathologic Anatomy—It has been conclusively proved that early in the course of true nephrosis there is no histologic change in the kidney This is true even when the full blown clinical picture is present Later in the disease the convoluted tubules of the kidneys are often dilated their cells show more or less advanced degenerative changes and large quantities of lipoid substances may be deposited in them These lipoids are often doubly refractive There is so much disagreement as to the "typical" histopathology of the glomerulus in true nephrosis that it hardly need be mentioned in a brief textbook discussion The changes in the tubules are definite in the glomeruli variable and slight There are no consistent changes outside the renal area and the cardiovascular system remains quite normal except for scattered atheromatous plaques

Clinical Picture—The average case of true nephrosis (and there is little deviation from this average) is characterized chiefly by the insidious development of generalized edema first gravitational and later an anasarca with fluid in the serous cavities There are no typical symptoms other than the mental and physical discomfort dependent on the monotonous and interminable existence of distended water logged tissues The duration of the disease varies from a few weeks to a few years but the patient eventually recovers and in most instances remains permanently well There may be several remissions during the course of the disease but the albuminuria rarely disappears until the cure is complete Fatal outcome when it occurs is usually due to secondary infection particularly invasion by the pneumococcus peritonitis being the common complication There is little doubt that the sufferer from true nephrosis has some specific lack of resistance to this organism

Physical examination in cases of true nephrosis is negative except for massive edema

Arterial blood pressure is rarely elevated but occasional readings above 150 mm (systolic) do not necessarily imply the presence of glomerulonephritis

The *urine* always contains large quantities of albumin There may be few or many white blood cells but rarely red blood cells Casts may or may not be found Doubly refractile lipoid bodies are seen in the urinary sediment in many of these cases They are not of special diagnostic significance for they appear in the nephrotic stage of glomerulonephritis also

Chemical examination of the *blood* uniformly reveals a low total serum protein content (usually below 4 per cent) and partition of these proteins shows that the serum albumin is greatly reduced with little accompanying change in the globulin fraction Lipemia in individuals with albuminuria has long been observed Bright in describing a typical patient said The serum is milky There is an increase in both fats and lipoids but for practical purposes an estimation of blood cholesterol is the most satisfactory clinical test Most cases have more than 200 mg per cent of cholesterol in the blood while some may have above 1000 mg Blood urea and total nonprotein nitrogen concentrations are normal in most cases but a transient elevation of blood urea is not evidence against the diagnosis of true nephrosis Serum chlorides are above normal if altered at all whereas sodium and bicarbonate concentrations are little changed The erythrocyte sedimentation rate is greatly increased This is probably dependent on the changes in the protein and lipoid contents of the plasma and cannot be interpreted as evidence of infection

The lowered *basal metabolic rate* so commonly a part of the clinical picture of nephrosis occurs also in the nephrotic stage of glomerulonephritis and its significance is not well understood in either relation Patients with this finding can take large quantities of thyroid extract with very little effect on their disease or in some cases on the basal metabolic rate itself

Diuresis may occur spontaneously or a remission may follow an unrelated intercurrent infection such as tonsillitis It should be noted that these remissions may occur with little or no change in the serum protein levels a fact which indicates that other forces than those dependent upon a lowered osmotic pressure must play a role After the edema has gone it is usually apparent that great loss of weight has taken place At times the convalescent patient is genuinely emaciated Part of this weight loss may be due to loss of appetite a complication not infrequently seen in prolonged cases where the patients become greatly discouraged with the apparently endless edema

Differential Diagnosis —True nephrosis may be confused with amyloidosis of the kidney the nephrotic stage of glomerulonephritis syphilitic nephrosis and nutritional edema The nutritional group is easily distinguished by the history and the quick response to adequate diet The Wassermann test and other clinical manifestations of syphilis help in the diagnosis of syphilitic nephrosis as does the fact that the beneficial response to antiluetic therapy may be striking In amyloidosis of the kidney there is usually some other manifestation of amyloid disease or the focus of infection causing amyloid changes is so apparent that classification is relatively easy If further diagnostic aid is required an estimation of the rate of disappearance of congo red from the blood stream is helpful This substance when injected intravenously in appropriate amounts disappears very rapidly in cases of amyloidosis The rate is accelerated in true nephrosis also but when 60 per cent or more has vanished in one hour it is valuable evidence in favor of extensive amyloid infiltration

The most difficult differential diagnosis and one that at times is impossible is that between true nephrosis and the nephrotic stage of glomerulonephritis A satisfactory past history of acute glomerulonephritis contemporary evidence of acute glomerulonephritis (hematuria or red blood cell casts) or signs of advanced chronic glomerulonephritis (hypertension anemia decreased renal function) would eliminate any indecision But many of the individuals with glomerulonephritis display every part of the pattern observed in true nephrosis with no evidence whatsoever of renal damage other than albuminuria Then the final outcome of the disease gives the sole answer Sooner or later the patient who has uncomplicated neph

rosis is likely to recover but if he develops terminal uremia, the underlying process is glomerulonephritis

Prognosis —As has been stated the prognosis *of true nephrosis is relatively* good The writer has seen the duration of the disease vary from several weeks to several years In spite of their susceptibility to secondary infection over half of the patients recover and remain well Although other infections do occur, a large majority is due to the pneumococcus and peritonitis due to this organism is a common complication The use of chemotherapy in the treatment of pneumococcal infections will probably alter most favorably the mortality statistics in this disease

Treatment —The general treatment suggested above for the nephrotic syndrome is advisable in true nephrosis viz adequate protein intake and rigid sodium restriction Sodium chloride and sodium bicarbonate are in common use both in food and as home remedies in either instance they should be carefully excluded The so called salt substitutes are usually sodium salts of organic acids and are therefore likewise to be avoided Moderate restriction of water intake is probably helpful As was pointed out when discussing the nephrotic syndrome excessive protein feeding has not altered the serum protein levels in our experience Protein restriction however is obviously contraindicated for the protein needs of the *nephrotic patient are somewhat increased* by the excessive loss of protein in the urine

The value of bed rest is a practical judgment to be made in the individual case according to the amount of edema and general well being of the patient Thyroid administration is a common custom when the basal metabolism is low It is difficult to see any benefit from it in the average case The apparent hypothyroidism seems to follow the course of the disease rather than to participate in its initiation

When an *extreme degree of edema in itself* produces symptoms *diuretics* may be used The most effective type of such therapy is found in the combination of a saline diuretic (ammonium chloride 3 to 6 Gm a day) with a mercurial diuretic (salyrgan or mercupurin at weekly intervals) If these drugs fail to induce a diuresis their use should be promptly discontinued in order to avoid mercurial poisoning Typhoid vaccine intravenously may cause a marked loss of edema in analogy to the diuresis occurring after acute infection Sweats and purges are useless and, indeed may be harmful An attempt to restore blood protein by transfusions is of little help and the beneficial effect of increasing plasma osmotic pressure by means of infusions of gum acacia is only transient

The crucial therapeutic problem in true nephrosis has been the prevention and treatment of the various pneumococcal infections to which these individuals are so peculiarly susceptible Most of the deaths in this disease have been caused by pneumococcal pneumonia peritonitis or sepsis The introduction of chemotherapy is undoubtedly the most hopeful recent contribution to the treatment of true nephrosis

The use of concentrated human serum (lyophil serum) is in an experimental stage and opinions as to its safety and value differ so greatly that its application to the treatment of nephrosis cannot be recommended at this time

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UREMIA

Definition —Uremia may be defined as a clinical pattern associated with renal insufficiency and nitrogen retention Although the uremic syndrome rarely occurs without evidence of maximal impairment of renal function it *has nevertheless* been long recognized that extreme degrees of nitrogen retention may not be accompanied by uremic symptoms and that there is no

constant correlation between the degree of nitrogen retention and the severity of the symptoms The renal insufficiency can be derived from any of the various ources of kidney damage such as nephritis bilateral renal infection mechanical obstruction of the ureters polycystic kidneys poison etc

The uremic state manifests itself in many ways but, for purposes of exposition one may indicate two major types of effect on the organism In one group are found the relatively well understood physiologic com plications of advanced renal insufficiency acidosis dehydration and disordered calcium metabolism On the other hand there are a large number of symptoms and signs that are apparently toxic in origin although the nature of these poisons has defied analysis In this latter group are found such phenomena as headache vomiting itching of the skin pericarditis and anemia

Manifestations Due to Renal Insufficiency.—The *acidosis* which occurs when the kidneys are damaged is dependent upon the important role that the kidney plays in relation to the acid base regulatory mechanism of the body The normal kidney has the faculty of manufacturing ammonia to serve as base for the acids that must be eliminated via the renal route In this way inorganic base is saved and the excretion of excess acid is furthered Phosphate excretion also aids in this process by virtue of the kidney s ability to form urine in which the ratio of the acid sodium phosphate to the alkaline phosphate is higher than that which occurs in the blood When the kidney fails to synthesize adequate amounts of ammonia and phosphate excretion is pathologically diminished two of the important stabilizing forces of the acid base equilibrium are impaired and acidosis occurs The blood CO_2 is then diminished and hyperpnea may result Severe acidosis augments certain of the toxic symptoms such as anorexia and nausea The electrolyte balance is altered in the same direction by loss of sodium Such base loss is not uncommon and is due in part at least to the polyuria caused by loss of the power of urinary concentration

Sodium depletion and the loss of water which occurs with it as part of hyposthenuric polyuria lead to *dehydration* one of the commonest and most distressing symptoms in uremia Anorexia and vomiting markedly augment this tendency Replacement of salt and water in such an event offers an unusually fruitful type of therapy in this distressing syndrome

The serum calcium levels in uremia are often significantly below normal This change is ascribed to the increased phosphate content of the blood and may also be due to a lessening of the percentage of plasma protein if such decrease be present Obvious clinical *tetany* is an occasional complication to be found in the uremic state and certain workers feel that much of the muscular irritability and convulsive tendency is due to a disturbed calcium metabolism It should be noted that the concentration of ionized calcium can be diminished when the total amount appears normal by ordinary clinical determination Tetany may be precipitated very easily in severe uremia by relatively small doses of sodium bicarbonate given to combat acidosis

Urea retention is the most classic physiologic result of renal insufficiency It is by definition always present in uremia and may play a minor role in the causation of such symptoms as headache and nausea Ingestion experiments on human subjects do produce such effects but the blood urea concentrations in uremia evince no consistently parallel relationship to these symptoms Creatinine uric acid amino acids and other end products of protein metabolism are retained in the blood in uremia Their individual or collective relationship to the development of the syndrome is still in doubt

"Toxic" Manifestations.—It would be impossible to report the varied investigations devised to discover the poison that seems to play such an important role in uremia Urea was the first chemical entity proposed but it has long since been discarded as of no etiologic significance Various extracts derived from the blood of patients suffering from this syndrome have been injected into animals and certain toxic effects have been ascribed to them however no convincing solution has yet been presented The consensus of opinion mainly on inferential grounds is that the etiologic agent includes probably many end products of protein

metabolism such as the phenols and guanidine and is the summation of several components

The earliest and most *characteristic symptoms* of the uremic state are weakness and anorexia The patient tires easily and finds active life an increasing effort Anorexia is an important influence favoring weight loss *in fact it may be the only cause of the emaciation* seen terminally Nausea and vomiting are constantly lurking in the background and when vomiting finally appears it is difficult to control

Headaches may appear early, but while they are not infrequent their severity has been somewhat overemphasized Most uremic individuals however complain of dull sensations scarcely painful in the cerebral area

Disturbances in the mental state are varied and when present they offer evidence of an advanced disease Restlessness and insomnia may be practically uncontrollable in one individual whereas another will remain in deep coma Muscular twitching or convulsions are further evidence of central nervous system involvement although tetany may be responsible for a certain amount of muscular hyperirritability It is possible that the itching of the skin should be classified with the symptoms related to the nervous system

Stomatitis diarrhea with ulcerative colitis and membranous lesions of the larynx and trachea are occasional examples of the widespread damage that can appear in the uremic state

Severe *anemia* appears at some time in most cases of uremia It is not benefited by the liver extract which is specific for pernicious anemia Iron administration is equally futile Hemorrhagic tendencies are occasionally seen in severe cases *Pericarditis* is a common late complication No evidence of bacterial infection is available to explain the mechanism of the inflammatory changes It would seem to be another example of toxic damage

The clinical picture of uremia is hardly a characteristic one There may be only one symptom or sign or many Indeed nearly all of the various manifestations that have been enumerated may exist together In addition cardiac insufficiency coronary disease cerebral accidents and visual damage may appear due to underlying glomerulonephritis or hypertensive vascular disease

Extrarenal Uremia —This term has in recent years been applied to those conditions in which renal function is inhibited by a decrease in blood flow through the kidney dependent in most cases upon a contraction of circulating blood volume Dehydration and shock are the commonest clinical conditions producing this entity

Pseudo uremia —It is necessary to interrupt discussion of the uremic state in order to mention a syndrome of headache hypertension convulsions and other cerebral manifestations that occur in two diseases more or less unrelated This syndrome may be confused with true uremia but careful differentiation is necessary for proper prognosis and therapy In acute glomerulonephritis there may develop a rapid elevation of blood pressure accompanied by severe headache papilledema nitrogen retention coma or convulsions This condition is believed by some to be dependent upon edema of the brain It usually yields promptly to such measures as intravenous hypertonic glucose solutions phlebotomy or even lumbar puncture The oral and parenteral administration of magnesium sulfate represent another effective therapeutic approach Pseudo uremia is not a bad prognostic sign if the patient survives the immediate attack in fact such cases seem to evolve less often into chronic glomerulonephritis

The other example of false uremia is seen in hypertensive vascular disease It is less explosive in form here than when it is found in acute glomerulonephritis Headaches retinal pathology and convulsions may occur but nitrogen retention is not a necessary or very frequent accompanying sign There may be other cerebral manifestations such as personality and memory changes or transient paralyses and the suggestion that there are alterations in the cerebral circulation due to vascular spasm or actual damage seems reasonably supported by the evidence at hand Fishberg uses the term hypertensive encephalopathy to cover both the pseudo uremia of acute glomerulonephritis and of hypertensive vascular disease on the assumption that they have a common pathogenesis

Prognosis —The prognosis of true uremia is dependent upon the underlying cause of renal insufficiency When this cause is amenable to treatment as in the case with prostatic obstruction the outcome is favorable When however the basic problem is insoluble as in the case of chronic glomerulonephritis or nephrosclerosis the onset of uremia is an indication that a fatal termination is not far distant An increase in blood urea levels may precede such an outcome by many years and during the course of the disease *correlate quantitatively in a most* unsatisfactory manner with the seriousness of the condition Retention of creatinine on the other hand is found more frequently in the terminal stages of uremia and hence is a bad prognostic sign Other unfavorable manifestations are severe anemia pericardial friction rub or convulsions Prognosis as to duration of life should be very guarded for an occasional patient who apparently is in the terminal stage will have a long remission

Treatment —Therapy in uremia is wholly palliative An understanding of the disturbed physiologic mechanisms suggests certain rational therapeutic approaches If a patient is depleted of salt and water replacement should be effected by intravenous or subcutaneous saline solutions A saline infusion of 1500 cc will often prove of extraordinary benefit but cardiac damage is so common a complication of the uremias that it is necessary to exercise great care not to overload the heart The infusion should be given slowly and be constantly supervised for signs of heart failure When possible the function of the right heart should be measured by frequent venous pressure observations during the course of the injection A rapid rise in venous pressure indicates the necessity for changing from the intravenous to the subcutaneous route In the presence of manifest cardiac insufficiency clysis is the preferable technic The parenteral administration of salt solution should continue until urine volume is definitely increased or the appearance of edema proves that the fluid intake has exceeded the kidney s remaining functional capacity to excrete water The chief indication for active treatment of acidosis is the presence of distressing hyperpnea It may occasionally be combated by the ingestion of bicarbonate of soda by mouth although great caution should be employed to avoid the production of vomiting or alkalosis In the presence of nausea the parenteral route of administration is preferable Tetany is an indication for intravenous calcium therapy (calcium chloride 10–20 cc of a 5 per cent solution), and some clinicians recommend the use of this therapy for twitching and convulsions even when tetany cannot be proved Loss of concentrating ability by the kidney necessitates a *constantly high fluid intake in order to* maintain an adequate urine volume Fluid intake therefore should be carefully regulated

The dietary problem in uremia consists chiefly in overcoming a more or less severe anorexia Any food that will interest the patient without upsetting his gastric equilibrium is valid material for his menu One should strive for a normal well balanced intake Effective protein restriction requires such an increase in total calories that it is rarely feasible and indeed is of little therapeutic value at best No degree of salt restriction is indicated in the absence of edema

The only effective treatment for the anemia is transfusion The use of this expensive procedure in a purely palliative role is a matter for practical decision in relation to individual problems Usually liver extract and iron do not help the uremic patient suffering from anemia

One of the most perplexing situations that can arise in the treatment of uremia is found in the incorrigibly restless patient Fortunately this is an infrequent complication Large doses of chloral hydrate bromides barbiturates morphine and hyoscine may be of little or no avail Even intravenous paraldehyde may be of only temporary aid

When cardiac insufficiency complicates the uremic state all other therapy must be considered secondary to the treatment of this defect It is unwise however to bleed a uremic patient with anemia unless a grave emergency exists Digitalis morphine and oxygen are used here in a fashion identical with that recommended in the absence of renal insufficiency

Purgation colon irrigation and sweating are not only incorrect in theory but *in many*

instances are actually harmful to the very sick patients subjected to these drastic measures

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ANOMALIES AND MALFORMATIONS OF THE KIDNEYS

Definition —Anomalies of the kidney include deviation from the normal in number structure, and position the result of arrested or faulty embryonic development

Etiology —The metanephros, or permanent kidney develops from a bud on the posterior wall of the wolffian duct and the metanephrogenic cap of mesoblast The former grows cephalad and forms the ureter kidney pelvis and by dichotomous branching the collecting ducts From the latter develop the convoluted tubules Failure of union of these with the collecting ducts has been postulated as a cause for congenital cystic kidney, but this is probably erroneous The kidney pelvis is opposite the second lumbar vertebra in a 9 to 10 mm embryo and very nearly maintains this position in the adult With the straightening of the back and development of the pelvic curvature there is a tremendous lengthening of the ureter often spoken of as the ascent of the kidney The various anomalies of the kidney can be traced to interruption or aberration of development they are more common in males and tend to run in families

Morbid Anatomy —For purposes of description anomalies may be divided into those of number structure and position *Bilateral absence* (agenesis) of the kidneys is rare and of course incompatible with extra uterine life *Congenital absence of one kidney* is found about once in 1000 autopsies is more common in males and on the left side The ureter is usually absent The solitary kidney is hypertrophied and often diseased The presence of both kidneys should always be established before nephrectomy as more than one patient has died from the removal of a solitary kidney *Hypoplasia* of one kidney is not uncommon Only about forty two cases of *supernumerary* kidneys have been reported

The important abnormalities of form are due to fusion of the kidneys which may be at the upper or, more commonly, the lower poles (*horseshoe kidney*) throughout (*cake kidney*), or the upper pole of one kidney may be fused with the lower pole of the other Persistence of *fetal lobulations* is common and of no significance *Polycystic kidney* (*q v*) should also be included among congenital malformations

One (usually the left) or both kidneys may lie in the true pelvis or in the iliac fossa (*ectopic kidney*) When such an ectopic position is congenital the ureter is short and is distinguished from movable kidney by this fact and the fact that it cannot be replaced in the normal position Occasionally both kidneys lie on the same side of the spine *Aberrant blood vessels* are extremely common but only of surgical interest except when they cause hydronephrosis by pressure on the ureter

Anomalies of the ureter are not infrequent and include bifurcation at times with two pelves complete double ureter implantation in an abnormal position in the bladder or other part of the lower genito urinary tract

Symptoms —The frequency of renal anomalies (8 per cent of routine autopsies) and the increased susceptibility to disease of anomalous kidneys indicate its clinical importance Symptoms are usually due to infection stone or obstruction and are apt to become manifest in early adult life rather than in childhood A horseshoe kidney may occasionally give rise to abdominal symptoms due to pressure of the isthmus on vessels and viscera A pelvic kidney may interfere with parturition

Diagnosis —A presumptive diagnosis of an ectopic or fused kidney can sometimes be made by palpation of a mass Intravenous or retrograde pyelography however is essential for accurate identification

Treatment —In horseshoe kidneys division of the renal isthmus and nephropexy may give relief from abdominal pain Plastic operations or removal of diseased anomalous kidneys in isolated instances have been beneficial The advent of the modern urinary antiseptics has given better control of in

fections but complete cure of the infection is difficult where drainage is poor

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CIRCULATORY DISTURBANCES OF THE KIDNEY

Chronic passive congestion occurs most frequently in association with chronic myocardial disease occasionally from obstruction of the inferior cava or from pressure upon the renal veins themselves *Infarcts* may arise from thrombosis in the course of senile atherosclerosis but are usually due to embolism They appear as wedge shaped lesions with the apex toward the medulla either uniformly red or with a gray necrotic center and hemorrhagic border Healed infarcts are represented by deep scars Symptoms of small infarcts are often lacking or are overshadowed by those of acute infection or endocarditis Larger ones give rise to sudden pain in the flank and hematuria There is no special treatment and the prognosis is good as far as the kidney is concerned except when one of the main renal arteries is blocked Multiple large bilateral infarcts occasionally result in sufficient destruction of renal tissue to lead to uremia *Bilateral cortical necrosis* of the kidney is a rare condition occurring usually in the toxemias of pregnancy but occasionally during infectious diseases or after trauma The cortex of both kidneys is yellowish greasy and necrotic sprinkled with hemorrhages and accompanied by thrombosis of the intralobular arteries The symptoms are anuria or marked oliguria albuminuria hematuria and nitrogen retention The etiology is unknown but has been ascribed to vasomotor disturbances with vasoparalysis and secondary thrombosis

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NEPHROPTOSIS

(*Movable Kidney*)

Definition —The normal kidney is not fixed but moves slightly with respiration and with change of bodily position These normal movements are slight When the displacement is sufficient to allow the lower pole to be palpated on inspiration the kidney is said to be *movable* With greater degrees of mobility the kidney may descend so that the fingers meet above it or it may fall as low as the iliac fossa *Floating kidney* is one which has become intra abdominal and has acquired a more or less complete peritoneal covering Movable kidney is to be distinguished from ectopic kidney which is congenital and which cannot be replaced in the renal fossa

Etiology —Constitutional factors are important These include a shallow paravertebral fossa often associated with a long flat chest narrow subcostal angle and ptosis of other viscera (Glenard s disease) defects in the perirenal fascia and lack of perirenal fat Faulty posture relaxed abdominal wall following pregnancy and repeated trauma from coughing straining etc are contributory causes Increase in the size of the kidney from polycystic disease or tumor often leads to its displacement Nephroptosis occurs in about 20 per cent of women and 2 per cent of men rarely during childhood most frequently between twenty and forty years of age In women the right kidney is movable about five times as frequently as the left while in men one side is as frequently affected as the other

Morbid Anatomy —A movable kidney may be perfectly normal and symptomless When pathologic changes occur they are the result of interference with the blood supply or kinking of the ureter and are due to congestion or to hydronephrosis

Symptoms —The great majority of movable kidneys give rise to no symptoms Many patients particularly women who present

vague gastro intestinal, dyspeptic or nervous symptoms have a movable kidney But the relation of such complaints to the kidney is highly problematical and frequently calling the patient s attention to the kidney only aggravates the symptoms The degree of mobility has no relation to the type or severity of symptoms These are due to disturbance of the blood supply giving congestion and pain, or to obstruction of the ureter The pain is a dull ache or dragging sensation located posteriorly in the loin or in front over the kidney and is relieved by lying down It may not be present in the morning but comes on during the day and is aggravated by exercise menstruation and constipation Less commonly the pain is acute colicky severe and associated with nausea and vomiting or symptoms of shock retention of urine and increase in the size of the kidney (*Dietl s crisis*) When the occlusion of the ureter is relieved the pain ceases abruptly and is followed by the passage of large quantities of urine Occasionally colicky pain of similar severity may be due to twisting of the kidney pedicle with obstruction of the renal veins Other symptoms accompanying movable kidney as fever pyuria and frequency are due to complicating infection or to stone

Diagnosis —The position and mobility of the kidney are determined bimanually with the patient both recumbent and standing Intravenous pyelography with films taken in two positions is helpful More important than the determination of mobility is the question whether it is the cause of symptoms Urinalysis is of little help for it is usually normal When symptoms are of renal origin they are relieved if the kidney is replaced or can be reproduced by injecting fluid into the ureter Dietl s crises must be differentiated from attacks of renal colic due to stone the rarity of hematuria and frequency of polyuria at the end of an attack in the former and the shadow of the stone on the x ray film in the latter usually suffice

Treatment —In the majority of cases no treatment is necessary When symptoms are definitely related to the kidney an effort should be made to return it to its normal position and keep it there Postural exercises increased diet in an effort to add to the perirenal fat and an abdominal belt with or without a special pad below the kidney are conservative measures which are often successful Pyelitis, if present should be treated Surgical fixation (nephropexy) which fell into disrepute because of many failures to relieve symptoms has a definite place in selected cases Operation for a movable kidney will not relieve psychoneurotic symptoms Surgery should be restricted to patients whose symptoms are known to be of renal origin and in whom medical treatment has failed The chief indication is obstruction to the ureter and abnormality in the outline of the renal pelvis on urography With the improvements in surgical technic the results in properly selected cases are satisfactory in about 75 per cent

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HYDRONEPHROSIS

Definition —Hydronephrosis is dilatation of the pelvis and calices of the kidney with pressure atrophy of its substance the result of obstruction

Etiology —Obstruction of the urinary tract causes the greatest degree of hydronephrosis when it is partial gradual or intermittent When obstruction is sudden and complete no urine is secreted increase in intrapelvic pressure is less marked and renal atrophy may be primary or follow a hydronephrosis The obstruction may be anywhere along the urinary tract When below the bladder as in prostatism or urethral stricture the lesion is bilateral infection is predominant and the degree of hydronephrosis less marked The cause of the obstruction may be outside the urinary tract as neoplasms adhesions operative trauma aberrant blood vessels or pressure from a pregnant uterus The common causes of acquired obstruction within the urinary tract

are stone stricture spasm foreign body, and tumor Many cases are due to congenital abnormalities in the ureter or urethra Displacement of a movable kidney may be responsible Occasionally no obstruction can be found

Morbid Anatomy —The degree of dilatation of the pelvis and distortion of the kidney varies enormously At times the sac may contain several liters of fluid As the size of the sac increases the papillae first become flattened then the renal cortex is thinned until finally it is represented only by a thin shell of tissue The outer surface is irregularly lobulated while the larger blood vessels may form definite radial bands on the pelvic wall like the ribs of an umbrella The fluid in the sac is more or less like urine but contains far less urea than normal urine Secondary infection and calculus formation are common occurrences

Symptoms —There may be no symptoms from a slight degree of hydronephrosis In other cases there is vague pain in the loin which is not characteristic When the disease is more advanced the outstanding sign is palpable enlargement of the kidney Other symptoms are pain and tenderness When the obstruction is persistent subjective symptoms are slight and may be limited to dull pain The kidney seldom attains a large size and the urine is normal, for since the ureter is blocked no urine is derived from the affected side If the obstruction is intermittent there may be attacks of pain accompanied by a definite increase in the size of the kidney and oliguria with polyuria when the pain is relieved Accompanying this there may be hematuria When such attacks are severe they are usually due to a movable kidney and are known as *Dietl s crises* When the degree of hydronephrosis is more than minimal the function of the affected kidney is diminished and in advanced cases may even be abolished Hypertrophy of the other kidney may compensate for this defect so that symptoms of renal insufficiency do not develop In bilateral hydronephrosis kidney function is much diminished and uremia may develop When the obstructed kidney becomes infected (pyonephrosis) fever leukocytosis and pyuria are present in addition

Diagnosis —The intermittent type of hydronephrosis is recognized by the association of pain and renal tumor with oliguria and their simultaneous disappearance When the renal mass is large it may be mistaken for a kidney tumor, neoplasm of the retroperitoneal glands encysted ascites or enlarged gallbladder In women ovarian cyst may cause confusion, but is usually more movable Accurate diagnosis depends upon pyelography either intravenous or retrograde Pain of questionable origin may be recognized as renal if it is reproduced by distention of the pelvis at cystoscopy

Prognosis —This depends much upon the cause and degree of the hydronephrosis When unilateral and of moderate degree the condition may never produce serious trouble Spontaneous cure however does not occur When bilateral there is always danger of uremia Finally there is always the specter of infection with the development of pyonephrosis

Treatment.—The cause of the obstruction should be removed if possible This may involve dilatation of a ureteral stricture removal of a calculus or fixation of a movable kidney The sac can frequently be drained by means of a ureteral catheter If useful function of the kidney has been destroyed it is usually better to remove it

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BACTERIAL INFECTIONS OF THE KIDNEY AND URINARY PASSAGES

(Excluding Tuberculosis)

Definition —The term *bacterial infections* is used to describe diseases due to the actual presence of bacteria in the kidney and urinary passages

Etiology —Bacteria may reach the kidney by way of the blood stream (*hematogenous infection*) by way of the ureter or periureteral lymphatics (*ascending infection*) or possibly directly from the intestines by way of lymphatics especially those which run from the ascending colon and hepatic flexure to the right kidney Hematogenous infections are by far the most frequent While bacilluria may occur as in typhoid fever without detectable evidence

of renal infection the kidney does not filter bacteria and their presence in the urine indicates some degree of renal damage Infection of clinical importance occurs when bacteria come in overwhelming numbers or continuously or are particularly virulent or because of lowered resistance of the urinary passages due especially to obstruction The physiologic hydronephrosis of pregnancy frequently predisposes to pyelonephritis Trauma, either from without or as a result of instrumentation of the urinary tract, is a predisposing factor Infections of the kidney may be caused by almost any organism, but more than half of them are due to *Bacterium coli* Next in frequency are *Staphylococcus* and *Streptococcus* more rarely *Proteus vulgaris* and *Pseudomonas pyocyaneus* In rare instances infection of the kidney may result from invasion by *Actinomyces* and parasites such as *Filaria Bilharzia* or *Strongyloides* Infections of the cortex of the kidney are usually due to pyogenic cocci while those of the portions of the kidney nearer the pelvis and of the pelvis itself are usually due to the colon bacillus

Morbid Anatomy — The pathologic changes in the kidney and pelvis vary with the infecting organisms and the route of invasion Hemolytic streptococcal sepsis usually produces a focal glomerulonephritis or an acute interstitial nephritis In subacute bacterial endocarditis there are the characteristic focal embolic lesions in the glomeruli Staphylococcic infection is usually manifest as small abscesses most abundant in the cortex The rare unilateral *renal carbuncle* is usually associated with furunculosis, whitlow or some suppurative lesion of bone or joint Small abscesses may undergo resolution otherwise they tend to increase in size coalesce and may rupture either into the perirenal tissue leading to the formation of a *perirenal abscess* or into the renal pelvis when pyuria will appear

Other infections involve the renal pelvis (*pyelitis*) and medulla These are usually due to *Bacterium coli* and may be either hematogenous or ascending While it was formerly believed that *pyelitis* and *pyelonephritis* were distinct entities it is probable that infection of the pelvis rarely if ever occurs without some involvement of the collecting portion of the kidney tissue Clinically the term *pyelitis* is used to describe those cases in which the infection is not severe enough to lower the function of the involved kidney

Pyelonephritis may be acute or chronic and unilateral or bilateral In the acute stage, ureter and pelvis show various degrees of inflammation the mucous membrane is red thickened and at times shows small ulcers or a pseudomembrane While the kidney may appear normal grossly, microscopic examination reveals scattered patches of cloudy swelling necrosis or suppuration in the papillae and pyramids of the medulla When the disease is chronic the kidney presents areas of cloudy swelling suppuration, or scar formation the intervening parenchyma remaining comparatively normal in appearance At times there is a complicating diffuse glomerulonephritis or arteriolar sclerosis Under such conditions the kidneys are small with narrowed cortex and show distortion flattening and reduction in size of the thickened pelvis Dilatation of the ureter may or may not be present When destruction of kidney substance is sufficiently extensive death in uremia is inevitable

Symptoms —The symptoms of abscess of the kidney depend on their size and number Small abscesses occurring in the course of septicemia may give no localizing symptoms The sudden onset of chill fever pain in the loin and tenderness on palpation of the kidney or in the costovertebral angle should arouse suspicion of renal suppuration in the presence of known infection elsewhere in the body The urine may present no abnormalities save for the presence of the infecting organism on culture Extension of the infection into the perirenal tissue (*perirenal abscess*) gives pain and later swelling in the costovertebral angle pain on motion of the trunk or spasm of the psoas muscle The more chronic cases of this nature often present considerable *diagnostic difficulty* being confused with biliary disease when the right kidney is involved or with splenic lesions when the left

The symptoms of *acute pyelonephritis* vary greatly There may be no constitutional symptoms and no manifestation other than albuminuria and pyuria with some frequency or burning on urination In the so called typical attack the onset is sudden or may

follow a few days of malaise with chill fever of 39° C or more headache prostration pain in the loin which may radiate along the course of the ureter and leukocytosis as high as 20 000 or higher In some cases leukocytosis is absent Chills and remittent fever may last for several days The urine contains bacteria albumin and varying amounts of pus The largest amounts of pus are found when the renal pelvis and ureter are predominantly involved The reaction of the urine is neutral or acid when *Bacterium coli* is present alkaline with *Proteus vulgaris* Red cells are frequent in the sediment but gross hematuria is rare

Chronic bilateral pyelonephritis is more common in women and often begins as an acute pyelonephritis in childhood or during pregnancy In men it is usually associated with retention of urine secondary to hypertrophy of the prostate gland The clinical picture is variable and frequently the symptoms are so mild that the disease escapes recognition until the terminal stage A history of an acute attack followed by persistent albuminuria with intermittent pyuria should arouse suspicion Recurrent bouts of fever with headache lumbar pain and costovertebral tenderness are increasingly common as the disease progresses The urine is dilute increased in volume and contains a variable amount of pus and albumin As the disease progresses renal function becomes impaired and uremia ultimately terminates a picture which may be identical with that seen in other forms of chronic Bright s disease The progress of the disease is slow and patients may present elevation of blood nitrogen for years while remaining in relatively good health Hypertension occurs in only one-quarter of all cases but in those cases with impairment of renal function it is present in 50 per cent Usually the hypertension is not of the malignant type the majority of cases showing a systolic pressure of less than 180 Edema is rare except that due to heart failure *Chronic unilateral pyelonephritis* can usually be distinguished from bilateral involvement only by urologic study Its recognition however is important since hypertension may occur even with unilateral disease and its cure has followed removal of the diseased kidney

Diagnosis —The diagnosis of renal infection is rarely difficult if its presence is suspected Unexplained fever chills or malaise, bladder symptoms as frequency burning or dysuria should lead to further study Pus and bacteria in the urine obtained by catheter in the female are convincing evidence of renal infection These urinary abnormalities serve in particular to differentiate infections of the kidney from acute disease of other abdominal organs as the gallbladder or appendix In tuberculosis of the kidney the onset is insidious gross hematuria more frequent while dysuria and frequency are more prominent Bacteria are not found by ordinary methods but tubercle bacilli can be demonstrated in a smear of the urinary sediment or by guinea pig inoculation All patients presenting evidence of urinary tract infection of uncertain cause should have the benefit of x ray examination in order to rule out stone as a predisposing factor and if the infection persists urologic study including pyelograms to detect renal anomalies or partial obstruction with hydronephrosis Culture of the urine is essential for an accurate diagnosis of the infecting organism It is often impossible to diagnose a cortical abscess early in the disease until it ruptures either into the pelvis discharging pus in the urine or spreads into the perirenal tissues The diagnosis of perirenal abscess may be extremely difficult In the presence of pain in the costovertebral angle with muscle spasm and scoliosis the demonstration of a high fixed diaphragm obliteration of the psoas shadow or irregularity in the outline of the kidney by x ray examination are helpful Treatment of course is surgical The high incidence of pyelonephritis as the etiologic agent in severe renal disease indicates the necessity for thorough investigation of the urinary tract in all cases of impaired renal function

Prognosis —The prognosis in acute pyelonephritis is excellent the attack usually lasting one or two weeks The severity of constitutional symptoms however bears no relation to the time necessary for the disappearance of bacilluria and pyuria In pyelonephritis secondary to obstruction of the urinary tract or stone the chronic form of the disease develops with great regularity unless the underlying cause is removed

Treatment —Acute pyelonephritis with

fever should be treated by bed rest, a soft diet and liberal amounts of fluid 3000 to 4000 cc daily If the urine is highly acid the intense urgency and dysuria can often be relieved by making the urine alkaline The administration of the older urinary antiseptics such as methenamine (0.5–3 0 Gm three times a day), pyridium (0 2 Gm, three times a day) or acriflavine (0 3 Gm three times a day) did not strikingly hasten the sterilization of the urine Methenamine is effective only in an acid urine, so that the addition of sodium acid phosphate or ammonium chloride is often necessary The introduction of the newer urinary antiseptics, mandelic acid and the sulfonamide derivatives has proved to be a tremendous advance in the treatment of urinary infections, and they have superseded the older drugs almost entirely

Mandelic acid was introduced by Rosenheim as a substitute for beta hydroxybutyric acid which had been shown to be the bacteriostatic agent in the urine of patients on a ketogenic diet In order for mandelic acid to be effective it must be present in a concentration of 0.5 to 1 0 per cent and the urine must be strongly acid pH 5.5 to 5 0 It is usually given in doses of 3 Gm four times a day after meals for adults as calcium or ammonium mandelate the latter in the form of syrup or elixir The daily urine volume should be maintained at about 1000 cc to insure adequate concentration The pH of the urine should be tested with chlorphenol red or nitrozene test papers and ammonium chloride or nitrate 3 to 6 Gm daily may be given if necessary The drug is particularly effective for *Bacterium coli* and *Streptococcus faecalis B pyocyaneus Aerobacter aerogenes* and staphylococci also respond to treatment but less effectively In cases of infection with *Proteus vulgaris* it is usually impossible to acidify the urine sufficiently for the drug to be effective The drug causes toxic symptoms in a small percentage of patients, these are nausea and vomiting diarrhea and hematuria Treatment should not be continued for more than one or two weeks In the presence of advanced renal insufficiency with loss of concentrating power, it may be impossible to attain the necessary concentration of the drug in the urine as well as to lower the pH to 5.5 in spite of the fact that the patient may develop a severe acidosis The use of the drug is contraindicated in such conditions

The sulfonamide group of compounds in general has proved to be the most satisfactory therapeutic agent The effectiveness is due to the fact that the chief route of excretion is through the kidneys and in its passage a high concentration is attained in the urine With these concentrations which may be ten to thirty times higher than that obtained in blood a bactericidal as well as bacteriostatic effect is produced Consequently it becomes possible to cure infections of the urinary tract caused by organisms which in other tissues are not susceptible to the sulfonamides Of the variety of compounds introduced for clinical trial sulfanilamide sulfathiazole and more recently sulfadiazine have been of most value Sulfanilamide is most effective against *B coli* and less so against staphylococci and *B proteus* It is effective at any pH but more so when the urine is alkaline A concentration of 200 to 300 mg per cent of free sulfanilamide in the urine is required This may be obtained by the administration of from 2 to 5 Gm daily in divided doses at 4 or 6 hour intervals with an equal quantity of sodium bicarbonate A urine volume of 1000 cc is preferable but this may be increased if fever or symptoms of cystitis are present Sulfathiazole because of its efficiency against staphylococci *B proteus Aerobacter aerogenes* as well as *B coli* has definitely relegated all other antiseptics to secondary positions A much lower concentration in the urine is required 25 to 50 mg per cent being often sufficient for cure for many strains In the treatment of staphylococcus infection an alkaline urine is preferable but for *Streptococcus faecalis* the pH of the urine should be not greater than 5 0, regulation of pH is not essential for *B coli* Doses of from 1 to 3 Gm daily in divided doses are adequate in most cases Sulfadiazine has as yet not been used as extensively as the other sulfonamides but the early reports indicate that it may be more effective than sulfathiazole for *B coli B proteus* and *Pseudomonas pyocyaneus* but of less value for staphylococci Two to 4 Gm daily in divided doses may be given Other sulfonamides such as

prontosil sulfapyridine and sulfacetimide have been advocated for the treatment of urinary infection but they have not been shown to be more effective than the three sulfonamides discussed

In using the sulfonamides the drug should be continued until two catheterized specimens of urine taken at four day intervals are found to be sterile to culture Usually a course of from one to two weeks suffices but smaller doses (1 Gm daily) may be given over longer periods of time (Helmholtz) especially where renal function is poor The sulfonamides should be administered with caution because of their toxicity Toxic manifestations include fever skin eruptions hemolytic anemia and neutropenia Sulfanilamide causes no renal complications but sulfathiazole may produce hematuria and nitrogen retention due usually to precipitation of the conjugated form in the tubules Although acetyl sulfadiazine is much more soluble than acetyl sulfathiazole renal damage may also occur even though less frequently Fluids should not be restricted therefore when sulfathiazole or sulfadiazine is used

In cases of *acute pyelonephritis* associated with stone or obstruction to the urinary passages satisfactory *treatment* of the infection may be impossible until these have been corrected by surgical means

The *treatment* of *chronic pyelonephritis* consists primarily in prevention and in the removal of obstruction and stones For the acute exacerbations of infection the sulfonamide derivatives appear to offer the best results and may at least delay the progress of the disease to the stage of serious renal failure If urologic study shows that the pyelonephritis is unilateral function of the other kidney is good and if there is an associated hypertension surgical removal of the infected kidney should be considered

The *treatment* of *perinephric abscess* and *renal carbuncle* like other accumulations of pus is surgical drainage

Infections of the Bladder —The bladder mucosa is strikingly insusceptible to infection so that in almost every instance *cystitis* is secondary to infection higher in the urinary tract to obstruction to the outlet of the bladder with retention of urine to genital infection or to trauma from stone or contaminated instruments When the primary cause is removed the infection clears up spontaneously The bacteria found are those mentioned under pyelonephritis In rare instances, the gonococcus invades the bladder the lesions being almost entirely confined to the trigone The pathologic changes are those of acute and chronic inflammation The symptoms are frequency, pain and pyuria Urination is more frequent during the day than at night The pain is usually described as burning is referred to the meatus and only gradually subsides after micturition has been completed In addition to variable amounts of pus there is not infrequently some blood present, especially in the last urine voided In chronic cystitis all symptoms are as a rule much milder Accurate diagnosis depends upon cystoscopic examination The most effective treatment consists in removal of the underlying cause Palliative measures include abundant fluids alkalinization of the urine hot sitz baths irrigation of the bladder and the instillation of the antiseptics such as colloidal silver preparation or 1 10 000 silver nitrate Oral antiseptics such as methenamine may be tried but are of doubtful value

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NEPHROLITHIASIS

(*Renal Calculus*)

Definition —The formation in the calices or pelvis of the kidney of concretions of crystalline urinary constituents which may be held together by a stroma of organic material

Etiology—Nephrolithiasis is about three times as common in males as in females and is most frequent between the ages of thirty and fifty It is said to be infrequent in the Negro Heredity is unimportant except with cystine stones which occur with an hereditary disturbance of metabolism Calculi are commonly composed of *uric acid urates calcium oxalate calcium phosphate* or mixtures of *calcium and ammoniomagnesium phosphate* more rarely of *calcium carbonate cystine* or *xanthine*

Calculi are formed from urinary constituents which remain in solution under normal conditions, why they precipitate in some individuals to form stones is obscure The theory that the constituents of the urine are kept in solution by the protective action of nonprotein colloids and that stone formation results from a disturbance of this equilibrium has not been supported by experimental work A number of contributory factors are recognized These include climate diet hyperparathyroidism disorders of metabolism and local conditions in the urinary tract especially stasis infection and marked changes in the reaction of the urine Stones are more common in hot dry climates where the urine volume is small than in more humid regions Excessive ingestion of nucleoproteins may favor the formation of uric acid stones and the excretion of oxalic acid is increased by a diet rich in rhubarb egg plant and certain other foods A high incidence of stone is reported in districts where the water contains a large amount of calcium carbonate Experimentally stones can be readily produced in rats by diets deficient in vitamin A But it is not clear whether these are due primarily to the vitamin deficiency or to infection changes in the epithelium of the pelvis relative excess of vitamin D or some other factor The relation of vitamin A deficiency to nephrolithiasis in man is undecided Probably inadequate or unbalanced diets are of more importance in the formation of stones in children than in adults The work of Albright has established the high incidence of stone in hyperparathyroidism with its accompanying hypercalcemia These patients may or may not show osteitis fibrosa cystica or osteoporosis This suggests studies of blood calcium and phosphorus in all cases of renal stone The *influence of abnormal* metabolism is also seen in the high incidence of stone in gout and in the rare cystine stones Feeding cystine to cystinuric patients however does not increase the excretion of cystine but the administration of the sulfur containing amino acids methionine and cysteine causes a marked increase in cystinuria Brand and Cahill believe that the error in metabolism consists *in failure of the proper handling of cysteine* derived from food and that cysteine is converted into cystine by the kidneys of the cystinuric patient Urinary stasis whether the result of obstruction in the lower urinary tract or of prolonged confinement to bed favors the formation of stones Infection not only provides a nidus of bacteria but because of the frequent association of alkaline urine favors the precipitation of phosphates *If urea splitting organisms are present* recurrence of stone is likely to occur in 75 per cent of cases Randall believes that calculus formation is dependent upon a preexisting renal lesion and has demonstrated areas of calcification without evidence of inflammation or infection in the renal papilla He believes that it is upon a nidus of this type that calculi of various composition develop

Morbid Anatomy—The size of the concretions varies from small particles like sand (*urinary gravel*) to large oval or branching (*stag horn*) calculi which fill the whole renal pelvis and branch into the calices Stones may continue to be formed and passed for years without serious kidney damage and with no more inconvenience than the attacks of renal colic Much more frequently, however movements of the stone lead to trauma to the pelvis or ureter with severe colic hemorrhage and secondary infection Persistent obstruction of the ureter leads to hydronephrosis or pyonephrosis with destruction of the kidney Stones are *bilateral* in about 10 per cent of cases and then almost always associated with infection A stone rarely persists in a normal bladder If the nucleus comes from above the potential vesical calculus is usually passed retention and growth in the bladder result from obstruction giving urinary stasis and residual urine Trauma inflammation of the bladder and infection follow

Symptoms —These vary with the size shape and position of the stone Minute smooth stones or gravel may be passed without symptoms A smooth stone fixed in one of the calices and unaccompanied by infection may remain for years without giving rise to either signs or symptoms Even a large calculus filling the entire pelvis may be symptomless The most common symptom is intermittent dull pain in the flank or back intensified by motion or a sudden jolt Abnormalities of the urine occur at one time or another in 80 per cent of cases of these albuminuria which may be minimal is the most constant while hematuria and pyuria each occur in about half the cases The classic attack of *renal colic* occurs when a stone is small enough to enter the ureter but large enough to obstruct it The pain is of excruciating severity begins in the back or flank and radiates first across the abdomen and then down along the course of the ureter to the genitalia and inner aspect of the thigh The pain is frequently sufficiently severe to induce nausea vomiting profuse sweating faintness and shock If there is infection there will be fever and leukocytosis in addition There is often frequency and urgency but the quantity of urine passed is small An attack may last only a few minutes but usually persists for several hours A patient may have but one attack of colic and pass the stone without further difficulty or with multiple stones there may be repeated attacks over a period of years After the attack is over the patient frequently complains of soreness along the course of the ureter and tenderness on palpation Palpable enlargement of the kidney is uncommon Albuminuria and microscopic hematuria are almost invariably present during the acute attack and may persist for several days Occasionally there may be gross hematuria

Intermittent or partial obstruction of a ureter or pelvis leads to the development of hydronephrosis and usually of secondary pyonephrosis with progressive destruction of the kidney If the condition is bilateral renal insufficiency and uremia may develop When the obstruction is complete it causes anuria from the affected kidney Complete anuria may occur with bilateral calculi, when one ureter is blocked if the function of the other kidney has been destroyed or with reflex inhibition of the unaffected kidney This last condition is rarely demonstrated and in some cases should be attributed to shock and low blood pressure rather than to a reflex

Diagnosis —In patients suffering from typical attacks of renal colic, the diagnosis can be made with comparative ease from the clinical history and is supported by the presence of blood or numerous crystals in the freshly voided urine A catheter specimen should be obtained in women Never-



Fig 108 —Retrograde urogram showing large oval calcium carbonate stone at the left uretero-pelvic junction (Courtesy of Dr Harry Hauser)

theless the diagnosis can only be established by x ray or pyelographic study for the pain is frequently not referred in the usual manner and may simulate that of appendicitis gallbladder disease peptic ulcer coronary thrombosis or even of disease of the vertebrae or spinal cord Similar colicky attacks of pain also occur in Dietl s crisis ureteral spasm and stricture and in pyelonephritis and renal tumor if the ureter is obstructed by pus or clotted blood When anuria is the only symptom it may be due to shock, stone nephritis or bichloride of mercury poisoning

Etiology—Nephrolithiasis is about three times as common in males as in females and is most frequent between the ages of thirty and fifty It is said to be infrequent in the Negro Heredity is unimportant except with cystine stones which occur with an hereditary disturbance of metabolism Calculi are commonly composed of *uric acid urates calcium oxalate calcium phosphate* or mixtures of *calcium and ammoniomagnesium phosphate* more rarely of *calcium carbonate cystine* or *xanthine*

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of the ureter or other manipulation with the ureteral catheter Stones in the pelvis can often be removed by pyelotomy but when there is marked renal destruction and large or multiple stones nephrectomy is advisable In spite of the best surgical technic and careful after treatment recurrence occurs in about 16 per cent of aseptic and 50 per cent of infected cases

J M HAYMAN JR

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AMYLOID DISEASE OF THE KIDNEY

(*Amyloid Nephrosis*)

Definition —A disease of the kidney due to the deposition of amyloid in the media of the arteries and glomerular capillaries and characterized clinically by albuminuria and edema

Etiology —Amyloidosis occurs almost exclusively in chronic cachexia most commonly in tuberculosis and in long standing suppuration as osteomyelitis empyema or lung abscess Rarely it occurs in the absence of suppuration in syphilis multiple myeloma or neoplastic disease The deposit was called amyloid by Virchow because it becomes walnut brown when stained with iodine it is a protein however and not a carbohydrate as suggested by the name Amyloid deposits have been produced experimentally by repeated injections of sodium caseinate bacteria heterologous sera and homologous globulin Considerable evidence has been brought forward to support the theory that amyloidosis is associated with hyperglobulinemia

Morbid Anatomy —Deposits of amyloid are most common in the spleen then in the kidney The amyloid kidney may be normal in size but is usually moderately enlarged The capsule strips readily revealing a smooth glossy or greasy surface On section the cortex is widened and the markings indistinct Microscopically amyloid is deposited in the vessel walls This is seen first along the inner surface of the basement membrane of the glomerular capillaries The final result is the conversion of the glomerular tuft into a bloodless amyloid sphere and consequent degeneration of its tubule The afferent arterioles frequently show deposits of amyloid between the cells of the media or under the endothelium The straight vessels of the cortex and the larger arteries are not involved as regularly or as early Occasionally amyloid is found under the basement membrane of the tubules otherwise the tubular changes resemble those of lipoid nephrosis In some cases there is sufficient destruction of nephrons to produce a small contracted kidney and renal insufficiency

Symptoms —Usually amyloid disease of the kidneys is of little clinical importance the picture being dominated by the under lying disease Albuminuria is usually present and an abnormal number of casts of all types except blood casts are found in the urine When the albuminuria is great enough to lower the plasma proteins the picture resembles that of lipoid nephrosis The urine volume however is usually greater and the specific gravity lower than in that disease Hypercholesterolemia is also less constant Hypertension and eyeground changes are unusual The edema fluid is of the nephrotic type containing 0.5 per cent or less protein A certain number of patients who live long enough develop nitrogen retention and renal insufficiency

Diagnosis —In the presence of tuberculosis or long standing suppuration if there is enlargement of the spleen and liver and

At times the shape and type of the shadows seen on an x ray plate are characteristic Cystine stones often coalesce to form large stones of a homogeneous wax like appearance Calcium oxalate stones may have a snowflake form with spicules radiating from a central focus Lamellar stones are usually phosphate in composition Large stag horn stones are either calcium phosphate calcium carbonate, or cystine Frequently the shadows are inconclusive Suspicious shadows may represent concretions in a vein or in the gut rather than in the urinary tract Uric acid urate, and cystine



Fig 109—A large calcium carbonate stag horn stone in the pelvis of the left kidney (Courtesy of Dr E Freedman)

stones often fail to give a visible shadow while denser calculi may be obscured by bone Intravenous pyelography may outline the stone but frequently ureteral catheterization and retrograde pyelography are necessary

Prognosis—The *prognosis in patients* with nephrolithiasis is extremely variable depending upon the size shape and position of the stone the presence of obstruction and of infection Small stones retained by gravity in the lower calyx may do no harm intermediate sized ones should be watched at intervals by means of the x ray while stones more than 1 cm in length are unlikely to pass spontaneously Irregularly shaped stones are less likely to be passed All stones tend to grow as long as urine is secreted by the kidney It is the general opinion that any stone retained in the upper urinary tract ultimately leads to the destruction of the kidney Renal calculus *is one of the* most common causes of infection and hydronephrosis, which may give rise to renal insufficiency uremia generalized sepsis or less frequently ulceration and perforation of the renal pelvis or ureter When anuria persists for more than a few hours the outlook is grave in the absence of surgical intervention When the conditions responsible for the formation of a stone persist after its removal recurrences are prone to occur

Treatment—While therapy depends upon the size and location of the stone and the presence of such complications as hydronephrosis infection and renal insufficiency general measures are of importance Fluid ingestion should preferably exceed 3000 cc daily in order to reduce the concentration of the urine The diet of patients with oxalate or uric acid stones should contain minimum quantities of these substances Such measures would be of more avail if stone formation were simply a matter of urinary concentration In the presence of infection (and provided renal function is good) mandelic acid or the sulfonamides may be of value in controlling this complication Cystine stones may frequently be dissolved by making the urine alkaline For this *purpose sodium* or potassium citrate, 1 to 2 Gm in solution three times daily may be used Treatment by vitamin supplement and acidification of the urine is still in the experimental stage, reported results still being inconclusive

For the pain of renal colic morphine in large doses is usually required A hot tub bath or local application of heat may help Atropine or nitroglycerin may be tried The *intravenous injection of* 15 cc of 10 per cent calcium chloride has been recommended but is not without danger

While expectant treatment may be adopted when there is a small stone and no infection in the *hope that it* will pass spontaneously the vast majority of cases require special surgical and urologic procedures At times a stone can be removed by dilatation

confined to the subcapsular zone The contents of the cysts are watery urinous hemorrhagic or viscid The pelvis and ureter are not obstructed but may be transformed to a mere slit The interlobular arterial branches show marked compression The disease is often associated with other malformations in the genito urinary tract or with cysts in the liver, and more rarely in the spleen and pancreas

Symptoms —If the degree of involvement is slight there may be no symptoms the condition only being recognized at autopsy When the reduction in renal substance is more extensive the symptoms are those of arteriolar nephrosclerosis diminished kidney function albuminuria polyuria low fixed specific gravity of the urine nitrogen retention anemia weakness and gastro intestinal symptoms Death is usually in uremia Cardiac failure is rare Hypertension and cardiac hypertrophy are present in the majority of advanced cases but less marked than in arteriolar nephrosclerosis The genesis of the elevated blood pressure may be similar to that which Goldblatt produced in dogs by constricting the renal arteries and be due to compression of the interlobular arteries by the enlarging cysts In other cases the presenting symptoms may be spontaneous painless hematuria which with a mass in the flank may lead to the erroneous diagnosis of tumor At times the passage of blood clots may cause renal colic Gross hematuria occurs in one third of cases At times the greatly enlarged kidney may give a dragging pain in the kidney region often increased by exertion and relieved by lying down The large polycystic kidney tends to slip down and in doing so may cause hydronephrosis by angulation of the ureter Sometimes it becomes infected

Diagnosis —Bilateral tumor of the kidney associated with hematuria or the symptoms of arteriolar nephrosclerosis offers little difficulty Only one kidney can be felt in about 20 per cent of cases and occasionally neither is palpable In all instances however the pyelogram is characteristic showing an elongation of the pelvis and calices with curved indentations caused by the individual cysts

Prognosis —In the newborn the disease is rapidly fatal In adults it may be latent for years and then progress rapidly to uremia or cerebral hemorrhage and death Occasionally intermittent hematuria or progressive renal failure may last for several years

Treatment —The treatment is chiefly medical identical with that for arteriolar nephrosclerosis Hematuria will usually respond to rest Puncture of the cysts to relieve pressure on the remaining parenchyma has not proved successful Nephrectomy should not be performed except for the most grave reasons such as infection or alarming hemorrhage and then only after



Fig 110 —Retrograde pyelograms in bilateral polycystic kidneys showing elongation of the pelvis flattening of minor calices and circular indentations due to the cysts (Courtesy of Dr E Freedman)

the other kidney has been shown to have fair function and to be only moderately involved in the cystic process

Other Forms of Cysts —*Multiple retention cysts* are common in the contracted kidney of arteriolar nephrosclerosis and chronic nephritis They are due to the occlusion of tubules by fibrosis Large *solitary cysts* are rare occur usually at the lower pole project from the surface of the kidney and may produce a dull dragging sensation accompanied by a palpable mass The fluid is usually yellow resembling blood serum or lymph It is not urine These cysts may be

albuminuria amyloid disease of the kidney should be suspected Glomerulonephritis in a cachectic patient may give the same clinical picture but red cells are present in the urine On the other hand the nephrotic syndrome without amyloid may of course exist in chronic disease The congo red test of Bennhold is of value in supporting a diagnosis of amyloidosis if it is positive This test depends upon the fact that the amyloid in the tissues takes up the dye and holds it for long periods Dye is injected intravenously and samples of blood are collected in four and sixty minutes From this the percentage of the dye disappearing in one hour can be calculated, in normal persons this is less than 60 per cent The test is useful as confirmatory evidence of amyloidosis if 90 per cent or more disappears in one hour A negative test does not exclude amyloid In chronic nephrosis the dye also leaves the blood stream with abnormal rapidity a large amount of it being found in the urine

Prognosis—The prognosis is that of the basic disease which usually leads to death within a year after the diagnosis of amyloidosis has been made But in some cases of tuberculosis of the bone or of syphilis, amyloidosis may last for years If the underlying cause can be removed as by amputation of a septic limb or treatment of syphilis the disease may become stationary or even regress Treatment is that of the primary disease An ample diet high in proteins is usually indicated for the primary condition and may combat the protein lost in the urine

J M HAYMAN JR

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CYSTS OF THE KIDNEY

By far the most common type of cyst of the kidney of clinical importance is *congenital polycystic disease* In this condition the normal renal tissue is in large measure encroached on and replaced by multitudes of cysts of widely varying size While always congenital symptoms usually appear either in infancy or between the fortieth and sixtieth years of life recognition of the condition is rare in childhood It is nearly always bilateral although one kidney may be more affected than the other The disease shows a decided familial and hereditary tendency

Etiology—The idea that cystic disease was due to failure of the embryonic convoluted tubules to unite with the collecting tubules *i e* that the cysts were retention cysts even without communication with the duct system seems to have been disproved by the studies of Kampmeier and of Norris and Herman The latter believe that for a long period in fetal life development of the kidneys is not abnormal Focal cystic dilatation of uriniferous tubules and collecting ducts occurring after differentiation of the metanephrogenic anlage and after the union of its elements with collecting tubules is followed by isolation of segments of these nephrons as cysts Increase in size of the cystic dilatations may result from the continued proliferation of epithelium and from rupture of septa and walls of tubules giving rise to anastomoses The increase in size of the cysts after birth usually brings about destruction by pressure and by vascular changes of whatever normally formed renal tissue exists These changes are thought to be degenerative since they resemble the stages in the normal degeneration of the mesonephros and of normally vestigial elements of the metanephros

Morbid Anatomy—The kidney retains its normal shape the degree of enlargement depending on the number and size of the cysts scattered throughout it Usually it is two or three times the normal size occasionally much larger The external surface is rough and knobby due to many closely set projecting cysts On section nearly all the renal tissue seems to have been replaced by cysts giving a honeycomb appearance The small amount of remaining parenchyma may be scattered irregularly between the cysts or

palpable mass is present in less than 20 per cent of early cases but as the tumor grows progressively can often be felt before death The growth generally preserves the usual shape of the kidney and may be uniformly smooth Very often it is irregular lobulated or nodular When the tumor is large the flank is deformed and the shape of the mass may be apparent on inspection Small tumors are frequently movable but the larger ones are generally fixed Varicocele may result from direct pressure of the growth on the left spermatic vein or from complete blocking by infiltration In rare instances marked circulatory disturbances with edema and ascites may occur from obstruction of the vena cava Fever is said to be present in 20 per cent of cases in those where no signs of *infection* can be detected Hypertension is found in 50 per cent of cases but is presumably coincidental since removal of the affected kidney produces no consistent alteration *in blood* pressure

Prognosis and Treatment.—The sole treatment of malignant renal tumor is nephrectomy which to be curative depends on early and accurate diagnosis Radiation in the opinion of most observers plays only an auxiliary role The presence of metastases or marked functional impairment of the opposite kidney contraindicates surgery X ray of the lungs and long bones for metastases should be performed in every case before surgery is attempted The *prognosis* of renal tumors is poor Less than 20 per cent of cases recover from malignant renal disease The immediate operative mortality is about 15 per cent 20 per cent are found to be inoperable and about 45 per cent die of metastases within a year or two

J M Hayman Jr.

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either congenital or acquired Tubular obstruction and ischemia are two of the known factors responsible either for their production or the rapid increase in growth Treatment consists in complete removal of the cyst, or drainage with destruction of the secreting membrane *Echinococcus cysts* occur in the kidney in 2 per cent of infestations They are unilateral and give only the symptoms of a slow growing tumor unless rupture occurs If rupture is into the renal pelvis the passage of the cyst contents down the ureter often provokes the symptoms of colic, or hematuria and for a time hooklets may be found in the urine Much more rarely the cyst ruptures into the intestine or peritoneum leading to pyonephrosis or peritonitis Such cysts are usually discovered by accident and require no treatment Ruptured cysts are prone to infection and therefore require nephrectomy

J M HAYMAN JR

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TUMORS OF THE KIDNEY

Neoplasms of the kidney may be primary or metastatic the former either benign or malignant They may be classified also according to their origin from renal parenchyma or from the urinary passages

Morbid Anatomy—Benign tumors rarely reach a size of clinical importance and include fibroma lipoma, angioma and adenoma Some adenomas are believed to be of embryonal derivation while others apparently arise as the result of regeneration following chronic fibrotic disease in the organ Malignant tumors of the kidney occur at two widely separate periods of life from birth to five years and after forty The common malignant tumor of childhood is the *embryonal nephroma* (*Wilms' tumor*) This tumor grows rapidly so that when first seen *it may fill the whole side of the* abdomen The commonest malignant tumor of adults is the *nephroma* (hypernephroma) which arises in the cortex forming a rounded or lobulated mass which at first encroaches on the normal renal tissue by compression only Grawitz believed the tumor was derived from misplaced rests of adrenal cortex This theory has been challenged by Gasparian and many others who believe that the great majority of these tumors are derived from adenomata or arise more directly from renal epithelium and that they are really adenocarcinomas Other malignant tumors of the adult are *carcinoma simplex or adenocarcinoma* sarcoma and embryoma Tumors of the pelvis and ureter are much rarer and include *papilloma* of the renal pelvis which is benign in its earlier stages but possesses *malignant potentialities papillary carcinoma* and the *squamous cell carcinoma* usually found as an accompaniment of the irritation caused by stone or chronic infection

Symptoms—The three cardinal symptoms of renal neoplasms are hematuria pain and the presence of a tumor mass in the loin Unfortunately these are rarely present early, or they are so trivial that they are neglected by the patient and overlooked by the physician Hematuria is the most constant and outstanding symptom of tumor of the kidney In the renal cancers of adults it is usually the earliest symptom but, in Wilms tumor in children it is a relatively late manifestation The bleeding generally comes on insidiously and is characteristically intermittent lasting only a few hours or days Pain occurring in 50 per cent of cases is frequently inconstant and vague but may be colicky due to passage of blood clots or dull and aching as a result of distention of the pelvis or capsule Neuralgic pains which may be severe usually mean local spread of the tumor to adjacent nerve trunks Pressure on neighboring viscera may also produce pain gastro intestinal symptoms being not uncommon Metastases to bones especially the vertebrae femur humerus and skull may give rise to pain in those regions Metastases to lungs are usually silent A

spleens may be found that are apparently normal Its average normal adult weight is about 150 Gm

Movable Spleen —A movable spleen (*floating spleen lien mobile*) may be found in any part of the abdomen Osler cites one that was found in an inguinal hernia and I have found it in the pleural cavity Such a spleen may become fixed in the abnormal position by adhesions and present great difficulty in diagnosis Movable spleen is either part of a general enteroptosis (Glénard s disease) or follows the enlargement of chronic splenic disease the derangements caused by an abdominal malformation *Symptoms* may be absent or general (especially digestive or circulatory), and may be referred chiefly to some other organ that has been disturbed If the shape and notches of the spleen can be palpated *diagnosis* is easy The absence of the normal splenic dulness and the fact that the mass can be returned to the normal position of the spleen (in the absence of adhesions) are also of diagnostic aid *Treatment* is usually desirable to forestall com

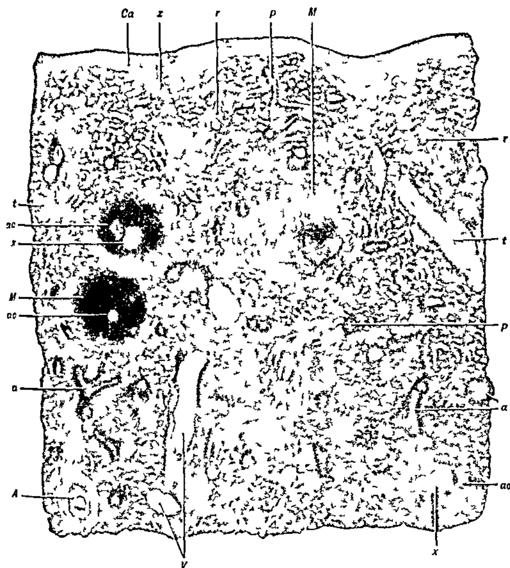


Fig 111 —Human spleen *Ca* capsule *z* origin of a trabecula from the capsule *t* trabecula A artery in a trabecula *a* artery covered by a sheath of lymphoid tissue *ac* central artery within Malpighian follicle M *x* germinal center V veins within a trabecula *r* red pulp penetrated by venous sinuses (blood of sinuses and veins not shown) *p* penicilli × 3° (Maximow Bloom Text book of Histology)

DISEASES OF THE SPLEEN AND RETICULO-ENDOTHELIAL SYSTEM

DISEASES OF THE SPLEEN

It has long been known that the spleen is not an organ necessary for life in fact the ancients, on the erroneous supposition that the speedy giraffe did not possess a spleen are said to have excised the spleens of runners in order to increase their efficiency Although since the time of Malpighi clinical and experimental investigations of splenic functions in health and disease have been numerous and ingenious it is only in the present generation that more concise concepts of its function have been obtained The author attempted in 1926 to assemble these in an article in Physiological Reviews since which time additions to knowledge of its functions have been neither negligible nor important

As the chief member of the hemolytopoietic system the spleen is unquestionably concerned intimately with blood cell formation and destruction Like the liver it may easily revert to its embryonic function of forming leukocytes and erythrocytes as occasion demands and it continuously forms *lymphocytes and* monocytes in common with other tissues Blood cell formation is also controlled indirectly by the spleen through its influence on the bone marrow Whether or not blood cell destruction begins within the circulation by fragmentation or by hemolysis the spleen is in either case directly concerned The fact that phagocytosis of cell debris or if necessary of whole cells takes place not only in the spleen but also in the other parts of the reticulo-endothelial system, may be taken as an explanation of the return to normal function after several months that occurs after splenectomy The spleen is probably also indirectly concerned with destruction of blood in other ways The clinical importance of this function especially when it is increased by disease is shown by the great diminution in the destruction of blood that follows splenectomy in hemolytic jaundice and pernicious anemia The unique vascular arrangements of the spleen (see Fig 111) produce potentialities for storage of erythrocytes (the red pulp) and action upon them (those in the splenic vein are less resistant to hemolysis than those entering by the splenic artery) and for rapid shunts that have significance in certain clinical conditions The reservoir function involving both elasticity and contractility which has been shown to *be practically important* under carefully controlled experimental conditions is probably of less importance in man than in the more muscular spleens of the animals studied

The majority of the accumulated evidence indicates that the spleen plays a role of some clinical importance *in relation to immunity* It has a selective affinity for bacteria fixes toxins and produces antibodies but here *also the spleen* cooperates with other tissues which can quickly assume these functions after its removal Its frequent involvement in infections is a clinical demonstration *of this* important relationship and the serious *lesions* that may result as for instance in tuberculosis syphilis or malaria are examples of the not uncommon phenomenon that on sufficient provocation an organ may become the chief victim of the very process which it is designed to combat A relation of the spleen to immunity is also indicated in *rats* infected with *Bartonella muris* where the *infection dormant* in intact animals is stimulated to a fatal course by splenectomy *Its* relation to tumor growth is also of interest Grafts in the spleen are said to take less frequently and to be smaller than elsewhere and intrasplenic inoculation apparently aids in raising resistance to tumor grafts elsewhere in the body Removal of the spleen also is said to stimulate the growth of tumors and to diminish resistance though the best recent evidence is against any special antineoplastic power in the spleen Positive experimental evidence of the spleen's protective power against bacteria has been difficult to obtain in recent years and still more so in the case of neoplasms where skepticism appears to be well justified

Secondary involvement of the spleen is important in many diseases whereas its primary diseases are few It will therefore be necessary here to mention briefly the splenic features of various diseases that are treated more fully elsewhere as well as the *primary diseases of the organ*

Anomalies of the Spleen —*In a few cases* the spleen has been found to be completely absent usually when there are other anomalies It may be subdivided into numerous splenunculi (as is normally the case in certain fish) or a spleen of normal size and shape may be accompanied by one or more accessory spleens These usually share in its pathologic changes and should *therefore be removed with* the spleen in such conditions as hemolytic jaundice Accessory splenic tissue may be found in such unexpected places as the stomach gall bladder testis groin and retroperitoneum Congenital abnormalities of position are usually due to or associated with other congenital defects deviations from the normal shape or size are seldom of clinical importance As the spleen is the most variable in size of the abdominal viscera large or small

infarct is found at autopsy An infected embolus causes a *septic infarct* rich in microorganisms with a characteristic serpiginous border and frequently terminating with the formation of an abscess It is much rarer than the simple infarct indeed this type was noted only four times in our series Infarction may be due to a thrombosis that is autochthonous in the splenic artery or retrograde in the vein A correct *diagnosis* is often difficult The commonest *symptom* is local pain especially if perisplenitis develops with tenderness over the somewhat swollen organ but, as has already been mentioned some acute splenic tumors partially twisted pedicles or abscesses also cause these symptoms *Surgical intervention* is not required unless continued chills and septic fever indicate the formation of abscesses The treatment otherwise is that of the underlying condition

E B Krumbhaar

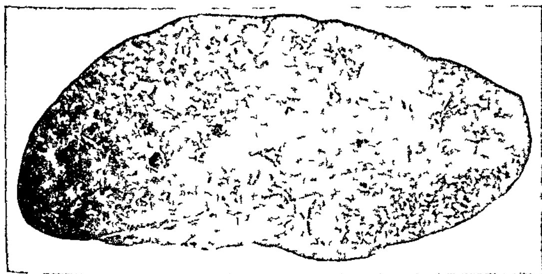


Fig 11 —Fetus Fleckmilz *Multiple nodules of necrosis and fibrosis resulting from arteriolar obstruction in a* woman of 59 suffering from generalized arteriolar sclerosis (Hosp U Pa Aut 42–17)

CHRONIC SPLENOMEGALY

(Amyloid Spleen Splenomegaly in Cirrhosis Tuberculosis Syphilis Malaria)

The various forms of chronic splenomegaly have certain pathologic features in common There is generally an early congestion and hyperplasia with obscuration of the malpighian follicles followed later by atrophy and fibrosis Splenomegaly also plays an important part in such conditions as the leukemias pernicious anemia Hodgkin s disease rickets to which sections the reader is referred

Amyloid Splenomegaly—Amyloid disease of the spleen is of clinical interest on account of its possible confusion with other types of chronic splenomegaly Caused by some chronic condition such as tuberculosis osteomyelitis and so on elsewhere in the body amyloid disease occurs more frequently in the spleen than in any other organ (156 times in the 5000 autopsies mentioned as compared with eighty three times in the liver and seventy eight times in the kidney) When the enlargement is *diffuse*—the sago spleen involvement of malpighian follicles being of pathologic interest only—the spleen may attain an extreme size and cause considerable disturbance by dragging or by pressing on surrounding organs *Diagnosis* is aided by the manifestations of a chronic disease elsewhere and by the signs of amyloid change in other organs (digestive disturbances enlargement of the liver urinary changes etc) The congo red test may be of diagnostic value in obscure cases especially if positive The *treatment* consists in general hygienic measures with the main effort directed against the primary disease Regression of the amyloid infiltration has

plications If a belt and pad or bandages prove unavailing operation is necessary In the presence of positive symptoms or the likelihood of recurrence, splenectomy is indicated

Torsion of the pedicle is a complication of *lien mobile* which usually causes acute violent symptoms demanding immediate surgical relief Sudden *pain and enlargement of* the spleen with signs of shock and often fever and vomiting are the characteristic signs A partial or more gradually produced twist causes less severe symptoms

Rupture—Traumatic rupture of a normal spleen is possible although this accident is usually found to occur in an organ that is diseased Rupture occurs more commonly in malarial splenomegaly, and may take place spontaneously during acute typhoid fever *especially if malaria has caused* enlargement, or after torsion of the pedicle Rupture has not infrequently occurred in therapeutically induced malaria Rarely one finds "spontaneous rupture of a normal spleen" in the sense that following some entirely inadequate cause (such as leaning over) the spleen ruptures and no recognizable lesion is found In one of our cases thrombosis of an intrasplenic branch of a sclerotic splenic artery was followed by a subcapsular hematoma with rupture and death from the extensive hemorrhage Agonizing abdominal pain was marked The *symptoms* resemble those of torsion with signs of internal hemorrhage Pain in the left scapular region and nonshifting paravertebral dulness are of diagnostic importance Rapidly increasing anemia and a marked leukocytosis may ensue *Surgical treatment* is of course imperative If the rupture is secondary to an infarct or abscess the symptoms of the primary cause are added and signs of general peritonitis soon develop

Referring to the infrequency of the three conditions above mentioned in our series of more than 10 000 autopsies the spleen in one instance was replaced by several splenunculi varying in diameter between 1 and 3 cm No cases of movable spleen or torsion and only three of rupture were encountered but such figures of course would vary greatly with varying material

Congestion and Acute Splenic Tumor—Because of the peculiar anatomy of the spleen as well as its functional relation to infections and toxemias active congestion occurs frequently The passive congestion of chronic heart failure or cirrhosis produces the familiar cyanotic induration The acute splenic tumor of infectious diseases is the commonest pathologic change found in this organ The spleen is probably enlarged *in all* acute infections of sufficient severity frequently to the extent of being palpable This is especially true of subacute bacterial endocarditis, when the pain and extent of sudden enlargement may be sufficient to cause diagnostic confusion with acute surgical conditions No special treatment for these secondary conditions is indicated

Abscesses of the spleen are usually multiple, are relatively rare, and usually result from the breaking down of a septic infarct More rarely abscesses may follow trauma or such infectious diseases as typhoid malaria phlebitis, and erysipelas In rare instances the whole organ may be converted into a sac of pus (Osler) Of fifty-one cases in more than 10 000 autopsies the infection was transmitted by blood or lymph channels in the majority by extension in some The *symptoms* are often subordinated to those of the primary source of the trouble until rupture and general peritonitis ensue or the condition may not be discovered until autopsy Sudden local pain and tenderness sometimes associated with the characteristic friction rub of perisplenitis and the usual signs and symptoms of severe suppuration may permit *diagnosis* *Laparotomy* is then indicated The prognosis is grave the operative mortality reaching 20 per cent Splenotomy may be preferable to splenectomy if many old adhesions are present

Infarction of the spleen occurs much more often than is recognized clinically It was found 202 times in a series of 5000 autopsies (140 anemic 62 hemorrhagic) but had undoubtedly occurred in many of these cases without causing symptoms or requiring special treatment In the *Fleckmilz* (spotted spleen) of *Feitis* multiple infarcts are produced by acute and chronic arterial disease (see Fig 112)

If caused by a sterile embolus the infarct is simple and usually anemic and is followed eventually by fibrosis and shrinkage Not infrequently however a fresh hemorrhagic

no means uncommon in the spleen the originally suggested mycotic etiology of this condition is denied by most

Kala azar —This tropical disease caused by *Leishmania donovani* is one of the commonest causes of splenomegaly in the Orient, the spleen may reach extreme size The enlargement is chiefly due to hyperplasia of reticulo-endothelial cells invaded by the parasite Identification of the parasite perhaps obtained by splenic puncture furnishes a sure *diagnosis* *Treatment* is naturally that of the underlying condition though in some cases splenectomy has also been found useful

E B Krumbhaar

TUMORS AND CYSTS

Tumors of the spleen although rarer than in most abdominal viscera are probably more common than is generally recognized The benign types—fibroma lymphangioma and hemangioma—are of little or no clinical importance I have seen however, a case of the last named where bleeding through the thin capsule required splenectomy and another where hemorrhage into the organ had produced a large cyst with pressure atrophy of most of the spleen Of the malignant tumors lymphosarcoma reticulum cell sarcoma and endothelioma may be primary whereas carcinoma is always secondary Some 200 primary tumors of the spleen have been reported in the literature Of the forty secondary malignant tumors in our series the primary site was in the breast in seven cases the stomach in five pancreas in three prostate in two and esophagus appendix lip and penis in one each There were twelve secondary sarcomata and one myeloma

Lymphosarcoma (which according to Custer is the commonest cancer of children) is also the commonest primary cancer of the spleen at any age It is composed of lymphocytes of uniform appearance and maturity the more immature the cell the more malignant the tumor and the more rapid the growth The inconstant signs (pain tenderness fever pressure phenomena blood count changes sensitivity to radiation and so on) may permit sufficiently early diagnosis for splenectomy to be curative Custer points out that splenic puncture should be avoided because of the likelihood of fungating growth from the wound

Diagnosis is usually made too late to permit effective treatment although a certain number of primary malignant tumors have apparently not recurred after removal by splenectomy Pain and a steadily growing mass in the left abdomen, with rather quickly developing anemia and emaciation are the traditional signs but these are by no means always present

Cysts of the spleen may be simple (congenital or acquired), parasitic or neoplastic and single or multilocular *Simple cysts* whether the result of trauma infolding of the peritoneum dilatation of lymph spaces breaking down of hematomata necrosis or infarction are comparatively rare Fowler has seen ninety eight nonparasitic cysts and Lombard and Duboucher have recorded 158 encysted hematomata Splenic cysts are most commonly found in women of child bearing age and the acquired types are thought to be usually associated with trauma When sufficiently large to attract notice the cysts usually appear as a slowly growing mass in the left hypochondrium and cause soreness and a dragging sensation If extensive calcification of the wall exists the diagnosis may be made by x ray Fluctuation is of course an important sign when present and a diagnosis can be made in some cases by tapping In general however exploratory laparotomy is preferable on account of the danger of spreading parasitic cysts over the peritoneum *Parasitic cysts* (echinococcus) are discussed elsewhere *Neoplastic cysts* are rare angiomata may assume cystic proportions while dermoid cysts are much more common than the two reported in the literature would suggest Dr Custer found five in 5000 autopsies Splenectomy is accomplished easily has never been reported to be fatal and should be performed if the symptoms warrant it

E B Krumbhaar

THROMBOSIS

Thrombosis of the splenic vein may be either partial or complete and produces symptoms that may be acutely fatal or may

lately been reported after cure of the primary disease

Cirrhotic splenomegaly is not infrequently such a prominent and early manifestation of hepatic cirrhosis that it produces special symptoms and is even thought by some to contribute to the cirrhotic process in the liver or at least to be due to the same toxic cause This is probable not only on account of the "upstream relation of the spleen to the liver in the portal circulation but also because successful removal of the spleen in such cases improves existing anemia and lessens the amount of ascites and collateral circulation Whether or not the obstruction to the portal circulation is the sole underlying cause enlargement of the spleen quickly becomes hyperplastic as well as congestive and according to Eppinger's theory of hypersplenism may well bring about an excessive destruction of erythrocytes and a consequent moderate or even severe anemia Disturbance by the cirrhosis of the liver's function as a storehouse of the antianemic substance will also be a contributory factor Some authorities regard this type of congestive splenomegaly as the chief variety of the Banti syndrome

Syphilis of the spleen, aside from the transient acute enlargement of the secondary stage may be either a diffuse fibrosis or, much more rarely gummatous and may occur either congenitally or as an acquired disease Syphilis is especially to be suspected in the splenic enlargements of early childhood *Diagnosis* depends on the combination of an otherwise unexplained splenomegaly with the signs or history of syphilis a positive Wassermann reaction and a marked anemia and tendency to jaundice and ascites *Treponema pallidum* has occasionally been found Although ordinarily part of the general luetic process and to be treated accordingly, syphilis of the spleen sometimes demands independent recognition *Treatment* in certain cases when the spleen continues to be enlarged and causes discomfort and when the positive signs of general syphilis remain after adequate treatment, the question of splenectomy arises As in syphilis of the central nervous system the exciting agent sometimes seems to be so protected (in a by path so to speak) that it withstands specific treatment and maintains an active focus of infection Successful splenectomy in such cases has sometimes permitted further treatment to become efficacious

Tuberculosis of the spleen, although a common secondary infection (606 instances out of 5000 autopsies) occasionally, like syphilis forms a resistant focus from which further infection continues to be disseminated In addition to the terminal miliary forms the spleen may be greatly enlarged by extensive infiltration with caseated or fibrotic tubercles or may rarely be the site of a single, palpable, nodular tuberculoma—often when no tuberculous lesions are demonstrable in other organs According to Winternitz this 'primary type attacks both sexes equally and at any age but is most often seen in patients from twenty to forty years of age In 70 per cent of fifty one cases reviewed pain and swelling of the organ were found usually with chronic digestive or respiratory disturbances fever weakness and emaciation An unexplained moderate polycythemia is sometimes found If tuberculosis is present or develops elsewhere correct diagnosis should often be possible On the other hand, the acute type with collapse fever chills and backache and the atypical forms present great diagnostic difficulty Except for the rather high postoperative mortality, splenectomy is said to be a satisfactory form of treatment

Malaria of the Spleen—In chronic malaria the spleen may reach great size As in syphilis and tuberculosis it may become a reservoir which resists specific treatment and permits the continuance of the disease In malaria as in kala azar the spleen because of its very function of destroying red blood cells is exposed to infection by the organisms which it liberates The large hard pigment laden spleen of chronic malaria need not be described here Attention should however be called to the numerous and complex adhesions which greatly increase the difficulties of removal Nevertheless splenectomy in selected cases has been followed by a consistently decreasing mortality and the patients who survive are greatly improved

A siderotic splenomegaly has been described (Gandy Gamna nodules) Marked fibrosis with iron and calcium deposits is by

Banti s concept than with the view that all congestive plenomegalies must be due to hypertension in the portal system

Morbid Anatomy —The morbid anatomic changes of the Banti syndrome are not especially distinctive The greatly enlarged hard spleen in early cases may show increase in the reticulum with a cellular hyperplastic pulp and degenerative changes in the follicular arterioles as well as congestion Later the follicles become small and scarce as fibrosis of the reticulum trabeculae and capsule increases Hemorrhages and infarcts are not uncommon The lymph nodes are normal the bone marrow hyperplastic and the liver (in the third stage) shows an ordinary peri portal cirrhosis

Symptoms —The disease according to Banti s concept usually begins in young otherwise healthy adults of either sex and if untreated proves fatal after several years The onset is insidious with a gradually increasing weakness and pallor Digestive disturbances and abdominal discomfort may first call attention to the enlarged smooth hard spleen The anemia is moderate and may be either microcytic or macrocytic in type the resistance of the red blood cells is slightly increased and the signs of active formation of blood cells are but slight Neutrophilic leukopenia is characteristic although leukocytosis may occur after hemorrhage or intercurrent infection Hemorrhage of obscure origin usually from the gastric veins or esophageal varices is not uncommon It may be fatal moderate and chronically recurrent or so slight as to be detected only by the presence of occult blood in the stools

Disregarding Banti s unrecognizable second stage his third stage is ushered in by the symptoms of cirrhosis of the liver with recurrent painless ascites occasional jaundice and increased anemia and emaciation The urinary changes are more marked and urobilin is present in increasing amounts in the urine and feces With marked terminal exhaustion fever and cardiorenal troubles are not uncommon After several months or a few years an intercurrent infection or hemorrhage causes death

Diagnosis —The diagnosis of Banti s disease is necessarily made chiefly by exclusion The various chronic splenomegalies mentioned, like *hemolytic jaundice* and *Gaucher s disease* have more or less distinctive signs and when the liver is cirrhotic a careful history of the order of appearance of symptoms must be chiefly relied upon to demonstrate the primary trouble The patient s age at time of onset anemia leukopenia and chronicity are guiding features of the disease *Portal* or *splenic vein sclerosis* or *thrombosis* or in fact anything causing increased portal pressure, may present an indistinguishable picture antemortem *Laënnec s cirrhosis* with an unusually enlarged spleen may cause diagnostic difficulties if first seen when the disease is well established *Hanot s cirrhosis* if there is any such condition is said to develop in even younger individuals and is differentiated by the large liver the greater tendency to jaundice and hepatic symptoms the abdominal crises and leukocytosis *Pernicious anemia* in the stage of remission *aleukemic stages of leukemia* and *atypical Hodgkin s disease* may present difficulties which usually disappear on prolonged study Under such circumstances it is obvious that the diagnosis will not infrequently be wrongly made antemortem or even sometimes postmortem The more careful and intelligent the study the less frequently will the error be made

Prognosis —Spontaneous recovery is unknown Exacerbations may alternate with minor impairment of health for a number of years sometimes more than ten until in the last stage definite invalidism supervenes Death often comes from ruptured varices

Treatment —If the operative risk is not too great and adhesions not too extensive *splenectomy* even in the third stage is by all odds the preferable treatment In preparation for this or if operation is inadvisable the usual hygienic and medicinal measures should be utilized Though most authorities have found that marked or even complete relief usually follows splenectomy cases have been reported that have been thought to show not only that the cause of the disease is not removed by splenectomy but that the patient may be no better off than before the operation Hemorrhages from cirrhotic varices may be helped by the operation though the patient otherwise improved by the operation is still liable to

persist for many years It may be due to trauma endophlebitis extension of near by infection pressure from tumors or adhesions and many other causes

Symptoms—As a result of the blockage the spleen becomes greatly congested and enlarged (600–1000 Gm) and the current in the gastric veins (*vasa brevia*) may be reversed (*i e* toward the stomach) This is apt to cause the copious and recurrent gastric hemorrhages which are such prominent symptoms In acute thrombosis sudden abdominal pain pallor weakness and signs of collapse may precede a fatal gastric hemorrhage In the chronic form there is frequently a recurrence of abdominal symptoms for several years, there are obvious gastric hemorrhages or occult blood is present in the stools and there is a tendency toward jaundice (complicating portal thrombosis) The spleen becomes palpable in spite of the accompanying ascites and the anemia and leukopenia are often disproportionately severe It is this combination which makes the differentiation from *Banti s disease* so difficult Gradually increasing phlebosclerosis may produce a similar picture If the thrombosis involves the mesenteric veins, hemorrhoids will be added to the picture and if the portal vein is involved *caput medusae* and other signs of collateral circulation appear The symptoms may on the other hand be obscure and confined to gradual abdominal enlargement so that preoperative diagnosis is nearly impossible *Diagnosis* is always difficult and is seldom made before death Recurrent splenic episodes are apt to be significant If a correct diagnosis can be made *splenectomy* should be performed

E B KRUMBHAAR

BANTI S SYNDROME

(*Splenic Anemia*)

Definition—By those who accept Banti s disease as a separate entity, it is regarded as a chronic disease of unknown origin primary in the spleen and characterized by splenomegaly anemia and leukopenia a tendency to gastric hemorrhage increased formation and destruction of blood cells and later by cirrhotic changes in the liver with ascites and jaundice To others it is a syndrome of varied etiology to some it is merely the result of increased pressure on the splenic veins

History—The term splenic anemia" was first used in 1866 by Gretsel in the case of a child with splenomegaly and anemia but no leukocytosis Through the articles of H C Wood Osler and others this group term gradually became familiar In 1883 Banti first observed that cirrhosis of the liver and primary splenic enlargement occurred together and later described different phases in a detail which is accepted by no one today

Etiology—Banti thought that the noxious agent was brought to the spleen by the splenic artery and a splenotoxin" In his original paper he emphasized the absence of detectable causes Of the various microorganisms that have been thought from time to time to play an etiologic role none is accepted today Except for the better ability to distinguish similar conditions therefore there has been no advance in the study of this problem for many years Most writers regard the Banti picture not as a specific disease entity but a syndrome that may be produced by a variety of causes some even wish to abolish the term entirely using some general term such as 'congestive splenomegaly" It should at least be accepted that conditions such as cirrhosis of the liver venous thrombosis etc which produce a long standing increase in pressure in the splenic or portal vein can produce a practically indistinguishable picture In favor of the separate entity view, however are differences in the general picture such as the early age of onset the considerable improvement that may follow splenectomy the occasional existence of splenomegaly before cirrhosis and disappearance of an observed cirrhosis after splenectomy Congestive splenomegaly has been occasionally reported without venous obstruction (Ravenna Arch Int Med *66* 879 1940)—regarded as an active congestion for which disturbances in the splenic arterial system have been suggested as a cause There is a type of congestive splenomegaly in children (see Arch Path *27* 935 1939) not as ociated with *disease or* obstruction of the splenic vein in which splenectomy usually leads to *recovery* In the absence of evidence of obstruction it seems no more difficult to reconcile this with

NaCl and is complete at about 0 34 In hemolytic jaundice the figures are from 0 04 to 0 16 per cent higher The number of reticulocytes is greatly increased (from a normal of less than 1 per cent up to 15 or 30 per cent even more than 00 per cent have occasionally been reported)

In the exacerbations especially marked and characteristic in the acquired form Widal s crises of deglobulization the patient may suddenly become seriously ill with fever abdominal pain increased anemia jaundice (nonobstructive), and leukocytosis Unexplained obdurate ulcers of the foot have been frequently observed and also osseous changes such as thickened enlarged frontal and parietal bones (Turmschädel) and mottling of the marrow spaces

Diagnosis —The decreased resistance of the erythrocytes to hypotonic salt solution is practically pathognomonic The blood findings (especially reticulocytosis and microcytosis) and acholuric jaundice should also aid in the differentiation of other forms of splenomegaly although the hemolytic type of pernicious anemia may present difficulties The presence of gallstones should not be allowed to mask the condition

Prognosis.—The danger to life is slight except in the exacerbations of severe cases In most instances however the damage to health is considerable

Treatment —Splenectomy has proved with but few exceptions to be a practical cure bringing quick and permanent relief of symptoms Accessory spleens should also be removed With the improvement in the recognition of the disease and its operative treatment the mortality has now fallen below 3 per cent Even this low death rate should suffice however to prevent surgical intervention if the patient suffers little or no inconvenience After splenectomy the blood count rises to or toward normal the jaundice disappears and the excretion of urobilin diminishes the resistance of the red cells usually increases but fails to become normal

Before splenectomy for the acquired form where the results are less satisfactory careful search must be made for the underlying cause If this can be removed the symptoms of hemolytic jaundice may also disappear If splenectomy is performed it is advisable to remove any removable intra abdominal chronic foci of infection at the same time Splenectomy should not be performed during an exacerbation if the individual can be tided over with drugs and transfusions Successful splenectomies however have been reported even during acute hemoclastic crises In Whipple s combined spleen clinic 13 of 17 splenectomies gave excellent results whereas 14 nonsplenectomized cases showed no improvement In his atypical group' i.e icteric splenomegaly secondary to other conditions splenectomy was a failure

E B KRUMBHAAR

MISCELLANEOUS CONDITIONS

Myeloid Metaplasia —In accord with its embryonic function the spleen easily reverts to blood cell formation on demand (myeloid metaplasia) This is most strikingly seen in osteosclerosis of the bone marrow and in erythroblastosis fetalis and Cooley s anemia It chiefly involves erythropoiesis It has been found after hemorrhage hemolysis and infection and has been produced experimentally by Custer

Under the name *Agnogenic Myeloid Metaplasia* Jackson et al have described a splenomegaly of unknown origin differentiated with difficulty from various other splenomegalies and important because in this type both splenectomy and irradiation are contraindicated

In *Hodgkin s disease* the spleen is rarely the primary site though it is not infrequently the chief site of involvement

Thrombocytopenic Purpura —In this condition discussed elsewhere the spleen plays an important if not altogether clear role Whether by destroying platelets or inhibiting their formation in the bone marrow —there is evidence for both these modes of action—the spleen appears to be the major offender and when it is removed the platelet count rises and signs and symptoms subside

Giant lymph follicle hyperplasia, a condition described by Brill et al is a precancerous condition of the spleen and or lymph nodes an item of special nosologic interest as it can apparently develop into either lymphosarcoma or lymphatic leu

fatal hemorrhage Ligation of the gastric coronary veins at time of operation lessens this chance Occasional emergency laparotomies for hemorrhage from varices have led to splenectomy, with consequent permanent improvement in the patient s general condition In A O Whipple s interesting spleen clinic splenectomy tried in thirty one cases of Banti s syndrome was followed by improvement in two thirds of the cases of Laennec s cirrhosis and with even better results in other cirrhoses splenic vein thrombosis and so on *Transfusions* are valuable if the anemia is severe or after dangerous hemorrhage If ascites is troublesome and diuretics prove useless *paracentesis* may be necessary *Talma s operation* (omentopexy) may be combined with splenectomy if cirrhosis and ascites are already present Ligation of the splenic artery is indicated where extensive adhesions or other complications do not permit splenectomy

E B KRUMBHAAR

HEMOLYTIC JAUNDICE

(*Spherocytic Anemia Hemolytic Splenomegaly Acholuric Hemolytic Icterus with Splenomegaly Cholemie Familiale Anemia Icterohaemolytica*)

Definition —Hemolytic jaundice is an inherited chronic disease primarily due to increased fragility of spheroidal erythrocytes and characterized by anemia increased destruction of blood cells acholuric icterus and splenomegaly

History —First observed by Murchison in 1885 hemolytic jaundice was established as a clinical entity by Hayem in 1898 Widal s empha is on the exacerbations or crises of deglobulization led to the differentiation of an acquired form known as the *Hayem Widal type* Two years later Minkowski recorded its familial occurrence and after Chauffard called attention to the fragility of the erythrocytes which is its essential feature the familial form became known as the *Chauffard Minkowski type* This name also included the isolated congenital cases The acquired type is now generally though not universally regarded as a dormant variety eventually recognized during an exacerbation

Etiology —The disease is due to an inherited weakness of the erythrocytes a trait dominant in the mendelian sense The small spheroidal erythrocytes have been shown by Haden to rupture more easily in hypotonic solutions and presumably also in the blood stream, because of their loss of biconcavity The *acquired form* the activation of a *latent congenital case* may be secondary to some acute infection (malaria tuberculosis syphilis dysentery cholangitis), but in many cases the exciting cause cannot be determined

Morbid Anatomy —The excessive blood destruction causes deposition of blood pigment throughout the hemolytopoietic system The spleen is greatly enlarged (500-1500 Gm), and the pulp and to a lesser degree the sinuses are much congested The bone marrow is hyperplastic if the anemia is sufficiently severe Gallstones probably due to inspissation of the increased bile secretion are common

Symptoms —Splenomegaly is often the first sign of the disease The size of the spleen and the abdominal discomfort increase during exacerbations The *jaundice* is distinct but not intense and is not associated with clay colored stools or with the presence of bile pigments in the urine *i e* it is nonobstructive Urobilin is present in urine stools or duodenal contents in greatly increased amounts constituting an important diagnostic sign The van den Bergh test and icterus index give high values the former being usually of the indirect type

The *anemia* varies greatly in different cases tending to be more marked in the so called acquired form of the disease The patient may be more icteric than sick (Chauffard) or may be incapacitated by an anemia that verges on the pernicious type In a series of the congenital type of hemolytic jaundice studied by me some years ago the red blood cell count averaged over 3 000 000 whereas in the acquired form it averaged about 2 000 000 in ten recorded cases it was below 1 000 000 The *quantity* of hemoglobin is proportionately low anisocytosis is marked and microcytes are especially common The cell volume is less diminished than the diameter the cells assuming a more spherical form (*spherocytosis*) The resistance of the red cells to hypotonic salt solution is greatly lowered Although this test varies somewhat with the individual and the method used normally hemolysis begins at about 0 44 per cent

conjunctivae commonly seen on both sides of the cornea' Skeletal changes—due to the presence of the characteristic cells in the long bones—have been detected roentgenographically during life and at autopsy A connection with amaurotic family idiocy has been observed

Diagnosis—While diagnosis is usually made on pathologic material the family history early onset great chronicity, size of the spleen and pigmentation of the skin may afford the clue Several times the correct diagnosis has been discovered by splenic puncture a procedure that is not without danger

Prognosis and Treatment—Splenectomy is the only treatment that has proved of value As the operative mortality is still rather high and the disease a very chronic one the operation should not be attempted without considerable thought If it is successful the chances for improvement are great although as the disease coincidentally involves other parts of the reticulo endothelial system complete cure is hardly to be hoped for If its progress outside of the spleen is sufficiently slow however the improvement may be lasting

E B KRUMBHAAR

NIEMANN PICK S DISEASE

(*Lipoid Histiocytosis*)

A disturbance of the reticulo endothelial system not unlike Gaucher s disease except that it occurs in young children is more severe and more quickly fatal and the characteristic large cells react to lipoid stains

This frequently familial condition is limited almost entirely to the Jewish race and occurs about six times as frequently in females as in males It usually begins in the early months of life and is accompanied by marked feeding disturbances with resultant undernourishment and mental retardation Spleen liver and lymph nodes will be found enlarged with some brownish pigmentation of the skin a slight but progressive anemia and moderate leukocytosis No treatment of lasting value has been discovered Death regularly occurs in the first few years of life from manition or intercurrent infection At autopsy the large foamy cells are found widespread through the reticulo endothelial system They give positive lipoid and negative iron stains Lecithin appears to be the most important abnormal constituent of the diseased tissues

E B KRUMBHAAR

HAND CHRISTIAN S DISEASE

The combination of exophthalmos diabetes insipidus and softened areas in the flat bones was first observed by A Hand in 1893 but escaped general notice until Christian s description in 1919 In some respects intermediate between the other two diseases its lipoid cell accumulations are chiefly in the flat bones those in the orbit causing the exophthalmos (which may be unilateral) and those at the base of the skull the diabetes insipidus Fibrosis may become a prominent feature The spleen and liver are often enlarged Anemia and hypercholesterolemia are characteristic The onset is in early childhood and without racial or familial predisposition Dwarfism is common and hemorrhages or fractures may lead to osteitis fibrosa The bony lesions are easily seen in the x ray (For details of diagnosis see table in Nelson s Loose Leaf Medicine) While no specific treatment is available good hygiene and low fat diet are indicated

GROUPS TWO THREE AND FOUR

Group 2 mentioned above (with hyperplastic changes in blood and tissues) includes at least one primary condition—*monocytic leukemia* (leukemic reticulosis) —and one secondary—*infectious mononucleosis* Both are noted elsewhere in this volume

In **Group 3** (hyperplastic changes in tissues only) are (1) the rather ill defined group of the aleukemic reticuloses (cp *non-lipoid histiocytosis* and *aleukemic monocytic leukemia*) and (2) the neoplasm *reticulum cell sarcoma* (retothelial sarcoma) Non lipoid histiocytosis is either to be associated with the leukemias or regarded as an obscure acute hyperplasia of cells of the reticulo endothelial system characterized by enlargement of lymph nodes or spleen a febrile course anemia leukopenia and thrombocytopenia and fatal termination First to be noticed in this condition may be the enlargement of cervical or other lymph nodes

kemia The huge follicles are distended with lymphoblasts

Splenectomy appears to be contraindicated in the leukemias the polycythemias, almost all cancers cirrhosis and most primary anemias (erythroblastosis fetalis etc) It is especially valuable in familial hemolytic jaundice and in thrombocytopenic purpura *though it can* be said that successful removal of the other chronically enlarged *spleens that have become obviously detri*mental is followed by improvement The decision to operate on the individual case must depend both on the state of the disease and the available surgical skill

E B KRUMBHAAR

DISEASES OF THE RETICULO ENDOTHELIAL SYSTEM

As a working classification of diseases of this system we may consider those with (1) *predominant lipoid metabolic changes* (2) *hyperplastic changes in blood and tissues* (3) *hyperplastic changes in tissues only* (4) *changes of unknown nature*

GROUP ONE

Gauchers Niemann Picks Hand Christians diseases and xanthomatoses can be best considered together as more or less independent lipoid diseases of the reticulo endothelial system (Aschoff 1913) those groups of cells of the spleen liver lymph nodes bone marrow lung and elsewhere that are especially concerned with phagocytosis various phases of immunity metabolism and so on Derived from cells in the reticulum and from specialized endothelium reticulo endothelial cells are here regarded as identical with the large mononuclear and transitional cells of the blood the monocyte macrophage histiocyte endothelial leukocyte and cells with various other names They aid in the disposal of effete erythrocytes bacteria and other particulate matter are increased in monocytic leukemia typhoid infectious mononucleosis and other infections and become stuffed with complex lipoids in lipoid nephrosis diabetic lipemia high cholesterol diet xanthelasma generalized xanthomatosis and the three diseases about to be mentioned

GAUCHERS DISEASE

(Large Cell Splenomegaly)

Definition —Gauchers disease is a rare condition characterized by chronic anemia and a marked splenomegaly due to peculiar large lipoid containing cells which are also found in other parts of the hemolytopoietic system

Etiology —First described by Gaucher in 1882 as a *primary epithelioma the changes* were later shown to be a specific form of endothelial or reticular cell hyperplasia the cause of which is now regarded as an inherited disturbance of lipoid metabolism

Morbid Anatomy —Although the cells typical of the enlargement can be found histologically in bone marrow lymph nodes and liver they are most abundant in the spleen This organ is greatly enlarged (average 3600 Gm) smooth a brownish red color perhaps interspersed with small yellow dots on section the normal landmarks are found to be obscured or invisible There are occasional minute hemorrhages or infarcts Histologically the characteristic cells are round and large (20–40 microns or more in diameter) with one or more small eccentric nuclei and much pale faintly acidophilic fibrilloid cytoplasm which does not react to ordinary lipoid stains but does *contain iron* compounds The lipoid has been identified as kerasin *although apparently* other lipoids may also be present

Symptoms —Gauchers disease begins insidiously in infancy or childhood usually before the thirteenth year with a predilection for females and Jews and pursues a very chronic course (average of twenty years) The enlargement of the *spleen* which may reach enormous proportions is sometimes *discovered accidentally* or as the result of local symptoms or else the anemia with its train of symptoms may be the first to become apparent The tendency to hemorrhages submucous or subcuticular the anemia and leukopenia are *all less marked* than in Bantis disease The liver may be considerably *enlarged in* advanced cases (Kupffer cells) though jaundice and ascites *are* rare The superficial lymph *nodes* are not enlarged A brownish discoloration *of* the skin has been noticed also a peculiar yellowish wedge shaped thickening *of* the

DISEASES OF THE BLOOD

INTRODUCTION

The blood normally consists of a circulating liquid plasma in which by virtue of its motion is maintained in suspension slightly less than an equal volume of corpuscles red cells white cells and platelets The function of the red blood cells is to hold in non diffusible form the hemoglobin essential for the transport of oxygen by the blood stream An important function of the white blood cells is to act as phagocytes to assist in the defense against infection The platelets are allied with the vascular endothelium in subtle ways necessary for the maintenance of its integrity Enzyme systems in the plasma provide a second line of defense for the blood vessels converting soluble fibrinogen to fibrin at the site of an injury Disorders of the blood and blood forming organs result in abnormalities of the corpuscular composition (anemias leukemias agranulocytosis and erythrocytosis) or of the coagulating ability (prothrombin deficiency and hemophilia) of the blood and in "spontaneous lesions of the small blood vessels (purpuras) permitting hemorrhage In addition are included conditions developing when the precursors of the adult leukocytes exhibit neoplastic growth usually (leukemias) but not necessarily (Hodgkin s disease) affecting significantly the morphologic composition of the blood stream In disease histologic changes occur especially in the bone marrow lymph nodes or spleen as well as in the circulating blood Conditioned by the fundamental features of the underlying blood dyscrasias may develop the secondary manifestations of deficient oxygen transport infection hemorrhage or invasion of vital organs by neoplastic processes

The fact that certain blood dyscrasias may to superficial examination successfully imitate cardiac renal nervous or even orthopedic conditions indicates that at least an initial determination of the hemoglobin level and an inspection of a blood film should be a routine diagnostic performance in every patient It is to be emphasized that as in any branch of medicine correlation of histologic findings with the results of history and physical examination is often essential for accurate diagnosis The microscopic examination of the blood and recently of biopsy specimens of the blood forming tissues has rightly occupied the attention of those interested in the study of blood dyscrasias Quantitative methods for describing the average volume diameter and hemoglobin concentration of the erythrocyte have replaced earlier qualitative estimates Supravital staining has increased the delicacy of microscopic methods for the identification of leukocytes To these descriptive aspects of hematology a physiologic orientation has been added by the demonstrated effectiveness of liver or iron therapy in appropriate types of nutritional anemia and the recognition that exposure in occupation or through chemotherapy to certain compounds containing the benzene ring may result in hemolytic or aplastic anemias agranulocytosis thrombocytopenic purpura or even leukemia

Anemia exists when the concentration of hemoglobin in the blood stream irrespective of the number of red blood cells falls below normal Consequently there are two great classes of anemia (1) those in which blood production though increased is less than the rate of increased blood loss or destruction (2) those in which for one of several causes the rate of blood production falls below the normal rate of blood destruction In certain anemias both classes of disturbance are involved and there is not general agreement as to the one predominating

In the first class of anemias physiologic hyperactivity of the bone marrow is usually reflected in the peripheral blood stream by increases in reticulocytes granulocytes and platelets An acute hemorrhage or hemolytic process causes an almost immediate increase in granulocytes and platelets but the reticulocyte response as in the restoration of nor

(less often of the spleen) or fever of septic type followed by weakness, prostration emaciation and occasionally jaundice of low grade The anemia shows a progressive decrease in *all* of the formed elements of the blood, there is usually a relative lymphocytosis but absolute lymphopenia Differential diagnosis from aleukemic lymphadenosis aleukemic myelosis, lymphosarcoma agranulocytosis tuberculosis and Hodgkin s disease depends finally on lymph node or bone marrow biopsy There is replacement of lymphoid tissue of the node with complete destruction of architecture through proliferation of both reticular and endothelial elements these are large pleomorphic (round to stellate) cells with basophilic polychromatic vacuolated cytoplasm often exhibiting phagocytic properties or with long delicate cytoplasmic processes' (Custer) nuclei are vesicular with from one to three nucleoli Giant cells are characteristic (Sternberg Reed or Langhans varieties), with cell infiltration of other viscera notably liver and kidney The treatment is still symptomatic with attempt to remove foci of infection Irradiation does not seem to be of any value

Reticulum cell sarcoma is a malignant neoplasm primary in the lymph nodes spleen bone marrow etc It is easily confused with other tumors or enlargements of these organs and undoubtedly many such cases were formerly called large round cell ' ' mixed cell or spindle cell sarcoma Its pleomorphic cells are in close contact with the delicate argyrophilic reticulum and its cytoplasm may even be seen joining the reticulum fibers Phagocytosis and Reed Sternberg types of giant cells are common It most commonly appears in a single chain of lymph nodes which rapidly become matted together with eventual metastases far or near

In Group 4 should be placed *Hodgkin s disease* (discussed elsewhere in this book) an important disease of obscure etiology

E B KRUMBHAAR

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blood fails to clot sufficiently rapidly to prevent bleeding from injuries to blood vessels too gross for platelet plugging

Erythremia characterized by a chronic and often marked increase in the concentration of circulating red blood cells and hemoglobin resembles the effect of chronic arterial anoxemia in experimental animals and in man In the idiopathic disease there is, however no degree of arterial oxygen unsaturation comparable to that in the so called "secondary polycythemias Reznikoff has presented histologic evidence for fibrosis of the capillaries of the bone marrow in polycythemia vera It is possible that this lesion may result in anoxemia of the bone marrow because of local stagnation of blood flow or interference with oxygen diffusion from the capillaries Others believe that polycythemia vera is a low grade neoplastic condition of the erythrocyte forming cells

The treatment of blood dyscrasias presents as striking contrasts in effectiveness as exist in any field of medicine Replacement of specific nutritional deficiencies by therapy with liver and stomach preparations or with iron is highly efficacious in nutritional macrocytic and hypochromic anemias respectively but is quite useless in other types of anemia Splenectomy removes the chief hemolytic organ in congenital hemolytic jaundice and so is regularly effective It may be useful in certain acquired types of hemolytic anemia especially when the spleen is large and the fragility of the red blood cells is increased Splenectomy is the only measure effective with some regularity in the treatment of thrombocytopenic purpura It fails in certain acute types and in any case the beneficial results may be only temporary Chemotherapy with quinine or sulfonamides in hemolytic anemias due to malaria or streptococcal septicemia respectively may be dramatically effective The sulfonamides deserve further trial in the control of infections especially of the oral cavity secondary to leukemia agranulocytosis and aplastic anemia Irradiation is a purely palliative though often valuable procedure For reducing the local lesions of lymphosarcoma or of Hodgkin s disease x ray therapy must be intensive By contrast is the increasing recognition that in the chronic leukemias the use of small amounts of more general irradiation given at regular intervals of a week or two is a suitable and safe method Radioactive phosphorus another form of irradiation has not yet been shown to have significant advantages over properly applied x ray therapy in leukemia Transfusion is a useful but purely passive form of therapy It neither stimulates nor depresses the hematopoietic organs By its use the blood volume may be augmented in severe hemorrhage and the hemoglobin may be increased in anemias with critically low values In thrombocytopenic purpuras platelets can be temporarily added to the blood stream and in hemophilia the clotting time of the blood may be temporarily reduced Transfusion does not raise the leukocyte count for more than an hour or two In addition specific or general therapeutic measures of value in other types of disease have their indications and their propriety in the treatment of patients with blood dyscrasias

W B CASTLE.

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ANEMIA

Definition —The term anemia is applied to any deficiency in the quantity or quality of the blood as manifested by a reduction in the number of red corpuscles or in the amount of hemoglobin usually in both

Etiology —In the past anemia has been

mal bone marrow function by liver extract or iron in appropriate anemias, begins only after three or four days and is maximal usually before the tenth day Increased blood destruction is usually evidenced by increased amounts of the pigment derivatives of hemoglobin bilirubin in the plasma and urobilinogen in the feces

In the second class of anemias, the bone marrow is assumed to be hypofunctional because of nutritional or endocrine deficiency toxic inhibition invasion by foreign cells or fibrous tissue or for unknown causes In general as exemplified by the blood picture in aplasia of the bone marrow, the reticulocytes granulocytes and platelets in the peripheral blood tend to be reduced in numbers Exceptions to this rule exist and the highly cellular bone marrow of pernicious or certain 'aplastic anemias may belie its apparent physiologic hypofunction Indeed certain authorities believe on the basis of bile pigment outputs that such anemias are in reality predominantly hemolytic in nature With certain exceptions, especially in the differential diagnosis of myelophthisic anemias including aleukemic leukemia and agnogenic myeloid metaplasia bone marrow biopsy despite its descriptive interest affords little information of diagnostic value which cannot be obtained by other means Critical observations on the percentage of reticulocytes during an initial ten day period should always be made following a suspected hemorrhage or acute hemolytic episode or when liver extract or iron is administered

Little difficulty in the diagnosis of the typical case of leukemia is encountered provided the blood is examined Clinically however especially in its acute forms and in children leukemia may assume the features of an infection and indeed may imitate other clinical conditions as diverse as pyorrhea arthritis or neuritis It is easily possible to fail to recognize the aleukemic forms and to confuse with leukemia such conditions as infectious mononucleosis marked leukocyte responses to infection or agnogenic myeloid metaplasia Some of the difficulty will be avoided if the fact is kept in mind that in the peripheral blood of leukemias should appear in addition to abnormal leukocytes evidences of disturbed erythrocyte production leading to significant anemia and abnormalities in the number of platelets In order to effect the differential diagnosis referred to above or to determine the nature of a process causing lymph node enlargement without diagnostic changes in the blood stream (e g Hodgkin s disease), lymph node or bone marrow biopsy or splenic puncture may be required

Certain cyclic compounds such as arsphenamine aminopyrine and the sulfonamides possess the property of producing in relatively rare instances serious toxic effects on the blood forming organs These are manifest as agranulocytic angina, thrombocytopenic purpura or aplastic anemia representing predominant injury to leukocyte thrombocyte or erythrocyte production individually or in combination It is clear that an unknown factor of individual susceptibility exists In other instances of these conditions but with a frequency which diminishes somewhat with the care employed in seeking a pertinent history no evidence of exposure to toxic compounds is found With the possible exception of the use of nucleic acid derivatives in agranulocytic angina the therapy of these conditions is unsatisfactory unless following removal of the offending agent or for unknown reasons there is spontaneous recovery

The pathologic physiology underlying the hemorrhagic conditions represents disturbances of individual components of a complex of physical and chemical factors In the normal individual if a small blood vessel is punctured it first contracts then blood platelets become adherent to the edges of the wound and finally the blood clots probably as the result of one or more enzymatic reactions which are set in progress by thromboplastic substances present at the site of injury The platelets then cause a firm clot by shrinking the strands of fibrin In the purpuras the clotting mechanism at least in the test tube is entirely or almost normal The defect is a congenital or acquired weakness of the vascular wall or a lack of platelets or a combination of both If prothrombin is deficient as in hemorrhagic conditions of the newborn or in certain instances of liver disease or if an unidentified enzyme associated with a globulin fraction of the plasma is deficient as in hemophilia the

are chiefly reticulocytes and often reach a peak of from 10 to 15 per cent on the fourth to seventh day Occasionally normoblasts and very immature leukocytes are seen The red cells are replaced more rapidly than the hemoglobin so that hypochromia results

Diagnosis—The history and often the continuation of hemorrhage the appearance of prostration and air hunger the weak rapid pulse and falling blood pressure and the characteristic blood picture of a leukocytosis and appearance of young red cells are all evidences of the loss of blood

Prognosis—The outcome of the condition depends entirely upon the amount and rapidity of blood loss the promptness with which treatment is started and the ease with which the hemorrhage may be stopped Thus if one third of all the blood is lost suddenly death may follow unless the fall in blood volume is immediately corrected although an individual may be deprived of almost two thirds of his blood within twenty four hours and still recover Ruptured gastric varices or an exsanguinating hemoptysis is stopped with difficulty while bleeding from an external wound is in most cases readily controlled

Treatment—The entire treatment of acute loss of blood consists in measures for stopping the hemorrhage and for immediately increasing the blood volume Unless contraindicated because the hemorrhage is from the upper portion of the gastro intestinal tract fluids should be given by mouth at once Blood pressure readings should be taken every half hour, and if the critical level (75 to 90 mm of mercury at systole) is approached emergency treatment should be instituted at once Transfusion of 500 to 1000 cc of blood from a compatible donor is the most efficacious form of treatment although bank blood and plasma or serum can be used with excellent results to ensure maintenance of a safe blood volume and in most cases much time can be saved by using these substances Temporarily saline may be injected intravenously or better still 300 to 500 cc of 10 per cent glucose solution followed by a hypodermoclysis of 1000 cc of saline The patient should be kept quiet If necessary morphine may be given Warmth is essential but care must be taken to avoid still further loss of fluid by perspiration If the blood volume can be maintained above critical limits and the hemorrhage stopped the majority of patients recover While iron may be given as a rule in a previously normal individual the substances which produce hemoglobin are ample in the body stores A high protein and adequate mineral and vitamin diet is desirable

Defective Blood Formation—*Classification*—Defective formation of blood may be due to one of the following

(*A*) Nutritional deficiency which may be subdivided still further into lack of
- 1 blood building substances such as iron and protein,
- 2 the materials effective in the treatment of pernicious anemia owing to a deficiency of either the intrinsic or extrinsic factor of Castle or of both,
- 3 thyroid secretion and, perhaps vitamin C,
- 4 possibly copper and other heavy metals

(*B*) Depression of the bone marrow by
- 1 chemicals such as benzol arsphenamine gold salts and the sulfonamides,
- 2 toxins elaborated in nephritis or in chronic infections,
- 3 physical agents such as x ray and radium and
- 4 mechanical interference as in leukemia Hodgkin s disease neoplasms and osteosclerosis

(*C*) Unknown causes, as in 'aplastic' or refractory anemia

Iron Deficiency Anemia—Iron deficiency occurs in (1) chronic blood loss (2) chlorosis (3) defective iron ingestion or difficulty of absorption (4) the removal of iron from the pregnant mother by the fetus (5) nutritional deficiencies in childhood (6) idiopathic hypochromic anemia and (7) gastro intestinal conditions for example following gastric operations idiopathic steatorrhea and hookworm infestation

The problem of adequate supply of iron and other substances necessary to produce hemoglobin and red blood cells has been demonstrated by Whipple and his co workers to be essentially one of balance During growth pregnancy and menstruation in

divided in two groups—primary and secondary—a classification based on the fact that the etiology of certain blood deficiency diseases was unknown Although this classification of anemia is still used, it is evident that any given case of anemia is secondary to one of the following three causes (1) loss of blood, (2) defective formation of blood (3) increased destruction of blood By the ordinary methods of examination, hydremia such as occurs in pregnancy would be included as a type of anemia The morphologic classification of anemias is of great value and depends upon the size of the red blood cell To determine this direct measurements of the diameter of the erythrocytes may be made or hematocrit values may be obtained and these compared to normal standards for given red blood cell counts Thus anemias may also be grouped as (1) macrocytic hyperchromic (pernicious anemia), (2) microcytic hypochromic (iron deficiency anemia), and (3) normocytic normochromic anemia (sudden loss of blood hemolysis) Many exceptions and varying combinations of these morphologic changes may occur but in most anemic patients the above classification is of great service in diagnosis Excellent classifications are available in the publications of Castle and Minot Vaughan and Wintrobe

Blood Loss —*Etiology* —Acute blood loss presents primarily a problem of reduced blood volume Although this results in anemia, the hemoglobin and red blood cell count in the absence of complications usually return to a normal figure within two months Acute blood loss takes place in traumatic severance of blood vessels rupture of viscera lesions of the gastro intestinal tract particularly gastric or duodenal ulcers typhoid fever and erosions of gastric and esophageal arterioles or varicosities hemorrhagic pancreatitis ectopic gestation placenta praevia pulmonary tuberculosis and after operations

Recurrent chronic blood loss is most frequently seen from hemorrhoids gastric and duodenal ulcers uterine lesions and gastric and esophageal varicosities occurring in cirrhosis of the liver Since anemia resulting from recurrent hemorrhage is to a great extent dependent upon the loss from the body of iron and other substances necessary for normal hematopoiesis a better concept of the mechanism underlying this condition is obtained if chronic blood loss is considered under the heading of "Defective Blood Formation' Therefore this description will deal with acute blood loss

Symptoms and Signs —The symptoms and signs of acute blood loss are very striking The patient feels weak and faint, becomes dizzy and quite thirsty and may vomit The *pulse* is rapid and weak the *skin* dusky, pale and cold the *temperature* subnormal at first and later may be slightly elevated and the *respiration* at first deep and rapid becomes weak and shallow The individual is *restless* and if hemorrhage continues delirium frequently ensues Finally a cold perspiration breaks out and the patient rapidly passes into a state of *shock* and coma During this condition the change in *blood pressure* is characteristic At first the diminution of the blood volume causes a reflex constriction of the arterioles which prevents any marked change in blood pressure and may even cause a slight rise With continued loss of blood the pressure declines gradually until at systole it is between 75 and 90 mm of mercury This is called the *critical pressure* If bleeding continues the pressure drops suddenly and markedly and shock supervenes All the symptoms and signs of acute loss of blood are due to anoxemia and depend upon a diminution of blood volume

Blood Picture —The immediate result of an acute hemorrhage is a decrease in blood volume The earliest change in the blood picture is a *polymorphonuclear leukocytosis* with an increase of immature polymorphonuclears (shift to the left) and of platelets which usually begins within fifteen minutes of an acute hemorrhage and reaches its peak within a few hours At first the concentration of red cells and hemoglobin remains about normal because the plasma volume is decreased Soon, with dilution of the blood by fluid drawn from the tissues the diminished quantity of erythrocytes and hemoglobin becomes manifest Following severe hemorrhage the greatest dilution occurs after two or three days or more if the intake of fluids is restricted the blood may not return to normal for two months Within the first forty eight hours after a brisk hemorrhage young cells appear in the circulation These

evidenced by a rise in the quantity of pigment in the serum bile stools and urine and an increase in the activity of the bone marrow which is made apparent by the presence of many young cells in the blood especially reticulocytes

While the immediate cause of hemolytic anemia is the destruction of erythrocytes in many cases the basic deficiency may be an abnormality of red blood cells so that they are easily hemolyzed

Classification—Hemolytic anemia may be due to (1) extrinsic and (2) intrinsic causes

1 Extrinsic (*a*) Chemicals—The use of coal tar derivatives and lead compounds are frequently associated with anemia The anemia of lead poisoning probably is due to the action of lead on the surface of the erythrocytes The cells become more fragile and are less able to withstand the trauma of circulation In Italy the raw fava bean or its blossom causes a severe hemolytic anemia in sensitized persons The sulfonamide drugs may cause a hemolytic anemia

(*b*) Infections—Hemolytic anemia is associated with hemolytic streptococcus infections and malaria Anemia occurring with most other infections is usually due to a depression of the bone marrow

2 Intrinsic Hemolytic spherocytic jaundice sickle cell anemia paroxysmal hemoglobinuria and acute hemolytic anemia of Lederer form an important group of hemolytic anemias

Hemolytic spherocytic jaundice is associated with splenomegaly and will therefore be discussed with the diseases of the spleen It is of interest however to point out here that the patient often suffers from a chronic anemia characterized by marked destruction of blood The spleen liver and kidneys become tinged with blood pigment there is a marked hyperplasia of the bone marrow and the number of microcytes and of reticulated cells in the blood is increased Although the diameter of the cells is small the volume of each cell is normal or greater than normal The young erythrocytes may come to constitute 25 to 30 per cent and even 90 per cent of the total number of red cells Bile is usually absent in the urine except during exacerbations but urobilin is present One of the characteristic features of this condition is the marked decrease in the resistance of the red blood cells to hypotonic saline solution Normal erythrocytes begin to hemolyze in a saline solution of about 0 45 per cent and are completely laked by concentration of 0.35 to 0.3 per cent In hemolytic jaundice hemolysis may begin at 0 7 per cent and be complete in solutions of 0.5 to 0 45 per cent The red blood cells are globular or spherocytic in shape instead of biconcave It is for this reason that they are less able to exist in hypotonic saline and are so easily broken up in the circulating blood

Sickle cell anemia occurs in Negroes rarely in white people is probably familial and is characterized by a reduction in the number of erythrocytes in the blood the appearance of sickle-shaped red cells rheumatoid manifestations leg ulcers bone changes and attacks of acute abdominal pain Patients suffering from this disease have a red cell count of approximately 2 500 000 a color index slightly below 1 a moderate leukocytosis and a distinct eosinophilia Nucleated red cells and some diffuse and punctate basophilia are commonly present Often the characteristic sickle shaped cells do not appear until after the blood has been allowed to stand for several hours or has been subjected to decreased oxygen tension and examined in moist preparations A specific lesion in this condition is described which consists of a malformation of the sinuses around the malpighian bodies of the spleen

Recently Dameshek has reviewed the hemolytic anemias and discussed such conditions as target cell anemia abnormal hemolysins the role of stasis especially in the paroxysmal nocturnal hemoglobinuria as described by Ham march hemoglobinuria and the very interesting condition of erythroblastosis fetalis studied by Levine and his co workers and shown to be due to immunization of an Rh negative mother by an Rh positive fetus with the production of agglutinins which cause hemolysis of the fetal blood cells

General Symptoms and Signs—These depend upon the condition from which the anemia results In general the patient feels weak tires easily becomes dyspneic on exertion and may complain of faintness vertigo and palpitation Pallor a rapid pulse

creased intake is necessary If any condition interferes with absorption there will be a deficiency of iron for the manufacture of hemoglobin It has also been shown that deficiency of protein will limit hemoglobin production even *if iron intake is adequate*

Although the classic type of chlorosis so commonly described in the latter half of the nineteenth century found in the Irish immigrant servant girl and associated with improper nutrition poor hygiene, hard work constipation and menstrual disturbances has practically disappeared, hypochromic microcytic anemia is a fairly frequent occurrence now in women between the ages of thirty and fifty This condition is usually associated with an achlorhydria or hypochlorhydria excessive menstrual flow harshness of skin or hair brittle convex or ridged fingernails and frequently with a glossitis When the sore, red tongue and dysphagia have dominated the picture this anemia has been called the Plummer Vinson syndrome Hematologically the striking features of iron deficiency from any cause whether it be from chronic hemorrhage or faulty intake are the relatively marked decrease of hemoglobin compared to the red blood cell reduction and the small size of the cells giving a low volume index usually less than 0 8

Pernicious and Other Macrocytic Anemias —Pernicious anemia and certain other macrocytic anemias are excellent examples of deficiencies of a red cell maturative factor which is contained in certain liver extracts These conditions caused by the lack of some nutritive material necessary for blood building will be discussed in the chapter dealing with pernicious anemia

Anemias Due to Lack of Thyroid Secretion and Vitamin C—Thyroid lack may cause a normocytic a macrocytic hyperchromic or an hypochromic anemia Bomford believes that the thyroid affects erythropoiesis only indirectly through its effects on the consumption of oxygen by the tissues and on gastric secretion Iron therapy for the hypochromic or liver extract for the hyperchromic anemia as well as thyroid substance are indicated

Recently vitamin C deficiency as a cause of anemia has been questioned It has been pointed out that hemorrhage and iron deficiency are frequently found in cases of scurvy and probably play the major role in the production of the anemia

Miscellaneous Anemias Due to Decreased Blood Production—The other causes of depression of bone marrow function such as the chemicals listed above nephritis chronic infections tertiary lues rheumatic fever subacute bacterial endocarditis and long continued sepsis as illustrated by empyema and osteomyelitis and the depression due to x ray and radium produce a variable picture When tumors crowd out the hematopoietic tissue as in multiple myeloma, metastatic carcinoma Hodgkin s disease and leukemia at first an initial irritation of the marrow may cause an increase of polymorphonuclear leukocytes platelets and young red cells but this may be followed by a blood picture suggesting hypoplasia

Aplastic anemia may be caused by certain intoxicating agents, chief among which are benzol radium x ray trinitrotoluol arsphenamine and the sulfonamides Occasionally it is associated with severe or chronic sepsis tertiary lues and arteriosclerosis, and recently nephritis has been shown to play an etiologic role The bone marrow may show aplasia or red marrow with fatty and fibrous replacement The fact that the peripheral blood suggests an aplastic bone marrow is no indication that this lesion will be found Careful study of bone marrow in so called aplastic anemia has shown great variability and frequently hyperplasia Of course even if the bone marrow presents a hyperplastic anatomic appearance it may be hypoplastic functionally The blood is deficient in red cells and hemoglobin but no hypochromia is present Lymphocytes predominate although leukopenia is invariable and thrombocytopenia marked A prolonged bleeding time and poor clot retraction are characteristic

The etiology of idiopathic aplastic or refractory anemia is unknown Rhoads and his co workers suggest abnormalities of the liver may occur which result in failure of detoxication of a possible endogenous toxic aromatic hydrocarbon This substance may cause hemolysis and bone marrow hypoplasia

Increased Destruction of Blood—Abnormal destruction of blood may vary from slight to severe Increased destruction is

evidenced by a rise in the quantity of pigment in the serum bile stools and urine and an increase in the activity of the bone marrow which is made apparent by the presence of many young cells in the blood especially reticulocytes

While the immediate cause of hemolytic anemia is the destruction of erythrocytes in many cases the basic deficiency may be an abnormality of red blood cells so that they are easily hemolyzed

Classification—Hemolytic anemia may be due to (1) extrinsic and (2) intrinsic causes

1 EXTRINSIC (*a*) CHEMICALS—The use of coal tar derivatives and lead compounds are frequently associated with anemia The anemia of lead poisoning probably is due to the action of lead on the surface of the erythrocytes The cells become more fragile and are less able to withstand the trauma of circulation In Italy the raw fava bean or its blossom causes a severe hemolytic anemia in sensitized persons The sulfonamide drugs may cause a hemolytic anemia

(*b*) INFECTIONS—Hemolytic anemia is associated with hemolytic streptococcus infections and malaria Anemia occurring with most other infections is usually due to a depression of the bone marrow

2 INTRINSIC Hemolytic spherocytic jaundice sickle cell anemia paroxysmal hemoglobinuria and acute hemolytic anemia of Lederer form an important group of hemolytic anemias

Hemolytic spherocytic jaundice is associated with splenomegaly and will therefore be discussed with the diseases of the spleen It is of interest however to point out here that the patient often suffers from a chronic anemia characterized by marked destruction of blood The spleen liver and kidneys become tinged with blood pigment there is a marked hyperplasia of the bone marrow and the number of microcytes and of reticulated cells in the blood is increased Although the diameter of the cells is small the volume of each cell is normal or greater than normal The young erythrocytes may come to constitute 25 to 30 per cent and even 90 per cent of the total number of red cells Bile is usually absent in the urine except during exacerbations but urobilin is present One of the characteristic features of this condition is the marked decrease in the resistance of the red blood cells to hypotonic saline solution Normal erythrocytes begin to hemolyze in a saline solution of about 0 45 per cent and are completely laked by concentration of 0 35 to 0 3 per cent In hemolytic jaundice hemolysis may begin at 0 7 per cent and be complete in solutions of 0.5 to 0 45 per cent The red blood cells are globular or spherocytic in shape instead of biconcave It is for this reason that they are less able to exist in hypotonic saline and are so easily broken up in the circulating blood

Sickle cell anemia occurs in Negroes rarely in white people is probably familial and is characterized by a reduction in the number of erythrocytes in the blood the appearance of sickle-shaped red cells rheumatoid manifestations leg ulcers bone changes and attacks of acute abdominal pain Patients suffering from this disease have a red cell count of approximately 2 500 000 a color index slightly below 1 a moderate leukocytosis and a distinct eosinophilia Nucleated red cells and some diffuse and punctate basophilia are commonly present Often the characteristic sickle shaped cells do not appear until after the blood has been allowed to stand for several hours or has been subjected to decreased oxygen tension and examined in moist preparations A specific lesion in this condition is described which consists of a malformation of the sinuses around the malpighian bodies of the spleen

Recently Dameshek has reviewed the hemolytic anemias and discussed such conditions as target cell anemia abnormal hemolysins the role of stasis especially in the paroxysmal nocturnal hemoglobinuria as described by Ham march hemoglobinuria and the very interesting condition of erythroblastosis fetalis studied by Levine and his co workers and shown to be due to immunization of an Rh negative mother by an Rh positive fetus with the production of agglutinins which cause hemolysis of the fetal blood cells

General Symptoms and Signs—These depend upon the condition from which the anemia results In general the patient feels weak tires easily becomes dyspneic on exertion and may complain of faintness vertigo and palpitation Pallor a rapid pulse

slight fever some dependent edema and systolic murmurs are often present As the changes in the blood depend upon the etiology and severity of the anemia no single description can fit the great number of variations which occur If the anemia has developed gradually patients may show very *few symptoms in bed with red blood cell* counts of 1 000 000 and hemoglobin values of 2 9 gm or 20 per cent

Blood Picture —Some of the most striking features of the blood picture in anemia have been mentioned in the description of each type The volume index may be a guide to the type of anemia present A low index implies lack of hemoglobin as seen in iron deficiency and chronic hemorrhage An index more than 1 suggests a defect in cell production and is characteristic of pernicious anemia It occurs however in sprue cirrhosis of the liver carcinoma of the pylorus pregnancy and other conditions

In most anemias due to defective formation of blood the hemoglobin reduction is greater *than that* of the red blood cells This is not true however, in the macrocytic anemias such as pernicious anemia unless iron deficiency complicates the condition Abnormalities of the white blood cells changes in size shape and staining properties of the red blood cells variations in platelets and in such properties as bleeding time and clotting time are variable and are taken up in the more comprehensive works to which the reader is referred In the hemolytic anemias the icteric index is increased but it is important to realize that in many anemias increase of serum pigment or pigment excretion may be due to hemolysis of *intrinsically abnormal red blood cells*

Treatment —The success of the treatment of anemia depends entirely upon whether or not the cause may be removed Anemia due to hemorrhage can be cured by stopping the loss of blood If necessary surgical intervention should be undertaken Frequently a supportive transfusion may be necessary before the patient can undergo an operation *Once the cause* of the hemorrhage is removed recovery is usually assured The patient should have the benefit of abundant fresh air sunlight and a nourishing diet which should contain spinach meat liver eggs apricots peaches *foods* containing vitamin C and sufficient proteins Administration of iron as well as of other

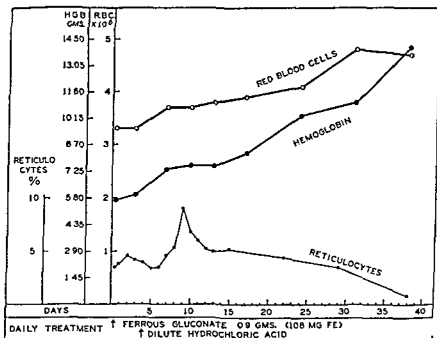


Fig 118 —The blood changes following treatment in a case of hypochromic microcytic anemia with achlorhydria and profuse menstruation (iron deficiency) Although the dosage of iron given was only about one-third that usually advised in such cases there was a satisfactory reticulocyte hemoglobin and red *blood* cell response

factors necessary for the production of hemoglobin and red blood cells may accelerate bone marrow function

The defective formation of blood due to leukemia or tumor invasion can only be treated symptomatically Usually as the leukemia yields to radiation or potassium arsenite the red blood cell and hemoglobin values rise When the condition is due to toxins such as benzol or when it is caused by sepsis these factors must be eliminated and supportive transfusions of blood employed

Iron therapy is indicated in all cases of hypochromic anemia and to be effective must be given in adequate doses While as much as 1 gm (15 grains) of iron daily has been advocated large amounts of iron may be retained even when relatively small doses are administered and Hahn and his co-workers found that in their experiments with radioactive iron absorption depends upon the body s need for iron Ferrous salts are usually more easily tolerated than ferric salts or reduced iron Ferrous sulfate 1.5 gm (22½ grains) iron and ammonium citrate 6 gm (1½ drachms) or reduced iron 1 gm (15 grains) daily are adequate doses A reticulocyte response within ten days presages a return of hemoglobin to normal within three or four weeks with proper therapy There is no justification for parenteral administration of iron Some patients tolerate large quantities of iron if the maximum dose is approached gradually Individuals frequently tolerate certain iron compounds and not others In general iron therapy tends to cause fewer gastro intestinal disturbances if given after meals There is some evidence that iron absorption is enhanced by the hydrochloric acid contained in the gastric juice Therefore in the presence of achlorhydria the administration of dilute hydrochloric acid with meals 2 to 4 cc (½ to 1 drachm) may be tried Liver therapy most effective when given parenterally should be undertaken in cases of macrocytic anemia due to nutritional defect such as addisonian pernicious anemia and in pernicious anemia of pregnancy This liver fraction is soluble in water and in 70 per cent alcohol A fraction which is insoluble in 70 per cent alcohol has been used by Whipple in the treatment of anemia in dogs subjected to blood loss The anemia complicating hypothyroidism must be treated with thyroid extract as well as the specific substance necessary for regeneration of hemoglobin or erythrocytes

The causes of blood destruction must be removed if possible This is relatively easy when the diminution of blood is due to some exogenous poison In infections the treatment depends entirely upon the eradication of the infecting organism Splenectomy is specific therapy for spherocytic hemolytic jaundice

In adults the administration of copper *salts and other heavy metals or large doses* of vitamins have as yet little evidence to support their use

In general the treatment of anemia consists first in removing the cause and then assisting the hemogenic function of the body which under normal circumstances is capable of maintaining an adequate supply of blood When such a procedure is impossible therapeutic measures including transfusions must be considered only palliative

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PERNICIOUS ANEMIA

(*Addisonian Pernicious Anemia Addison's Anemia Biermer's Anemia Primary Anemia*)

Definition —Pernicious anemia is a disease due to *deficiency in the body of material derived from food and manifest as a macrocytic anemia associated with disturbances of the gastro intestinal tract and frequently of the neural system If untreated* the disease progresses by relapses and remissions to a fatal issue Under adequate treatment with a suitable preparation of liver or *stomach the blood remains normal* symptoms but not all signs of disorder of the digestive system vanish and no progress or development of neural system lesions occurs

History —James S Combe of Edinburgh described a case of pernicious anemia in 1822 Thomas Addison of Guy's Hospital London recognized idiopathic anemia as a clinical entity in 1849 and published his best known description in 1855 in a monograph On the Constitutional and Local Effects of Disease of the Suprarenal Capsules" Anton Biermer of Zurich drew attention to the disease on the continent in 1872 under the name progressive pernicious anemia Treatment was universally unsuccessful until in 1926 Minot and Murphy discovered that the daily ingestion of large amounts (200 ± Gm) of mammalian liver was an effective remedy In 1928 Castle demonstrated the part the stomach plays in the causation of the disease

Incidence —*Pernicious anemia rarely* occurs before the age of thirty The majority of cases develop in the fourth and fifth decades of life and are about equally divided between the two sexes The disease occurs especially in the northern parts of the north temperate zone of America and Europe where there are probably not less than 35 cases per 100 000 population It is prone to develop in blue eyed individuals of the Nordic race whose hair has turned prematurely gray and who have broad facies and a large body frame On the other hand some patients show none of these features When complete family histories are available about 18 per cent of the patients will be found to have one or more close relatives who have or have had the disease

Etiology —There is an almost constant absence of hydrochloric acid in the gastric juice which may appear years before the anemia and almost always remains in spite of liver therapy The atrophy of the stomach responsible for this condition suggested to C Handfield Jones in 1855 and to Fenwick in 1870 that failure of digestion was responsible for the condition This idea became over shadowed by the conception of infective causes and mechanisms not involving the gastro intestinal tract The importance of gastritis, however was emphasized by Faber and Hurst and the idea that the condition represented a dietary deficiency arose about the time liver therapy was first studied Castle has shown that the disease is due to a nutritional deficiency conditioned by a defect in the gastric secretions and that this disease and certain other macrocytic anemias are related to a common etiologic mechanism The normal individual secretes a gastric (intrinsic) factor which reacts with a food (extrinsic) factor for the production of the supply of liver extract to maintain normal blood formation The material is absorbed and stored in the liver and certain other tissues In pernicious anemia during a relapse "liver extract" is essentially absent in the patient's liver The thermolabile gastric factor is secreted in man particularly from the fundic and cardiac portions of the stomach and in pigs especially from the pyloric portion and probably from the duodenum Its nature is unknown, it has not been identified with any recognized constituent of the gastric secretion *The thermostabile* food factor is present in a number of natural sources (meat eggs cereals etc) of the vitamin B complex Castle has represented the factors *involved in the* production of the substance that is deficient in pernicious anemia and related macrocytic anemias by the schematic formula

$$\frac{F \times G}{I} = LE$$

F stands for food factor G for gastric factor and I for intestinal impermeability or any defect causing malabsorption or alteration of those substances or a product of their effective interaction L E stands for "liver extract the independently effective thermo stabile factor found in mammalian liver Probably in none of the anemias produced by alteration in this mechanism is any *factor* on the left of the equation completely normal and there is a variable participation of defects of one or both of the factors in the numerator or some increase of the denominator value Any or all of such changes from the normal if sufficiently great will

create a decrease of "liver extract" and so produce macrocytic anemia which will respond to the parenteral administration of liver extract

If the dominant defect is in the food the anemia will vanish when either extrinsic factor or liver extract is fed Extrinsic factor deficiency occurs in some cases of pernicious anemia of pregnancy in certain cases of sprue and idiopathic steatorrhea and in unusual cases in the temperate zone which are often clinically indistinguishable from addisonian pernicious anemia The mechanism for the production of many cases of macrocytic anemia of the tropics is not clear These cases can be cured by crude liver extract but not with the purer liver extracts effective in pernicious anemia Autolyzed yeast is also effective in these cases but does not benefit patients with addisonian pernicious anemia If the dominant defect is in the gastric factor the anemia will not respond to the extrinsic factor but to liver extract This is typical of addisonian pernicious anemia The macrocytic anemia of fish tapeworm infestation presumably arises from alteration in factor E G or both If factor I is sufficiently increased the patient may respond to no type of material given by mouth but will respond to parenterally administered liver extract Thus defective absorption of necessary material may occur for example in sprue and prolonged diarrhea as from dysentery Intestinal stenosis and short circuits may lead to the picture of pernicious anemia perhaps by enhancing the absorption of products that impair the internal metabolism of liver extract Infections intoxications and severe damage to vital organs inhibit the effect of liver extract In different patients the action or optimal dose of parenterally administered liver extract may vary considerably

Increases of extrinsic factor and in residual amounts of intrinsic factor probably explain the spontaneous remissions of pernicious anemia formerly observed Complete recrudescence of the intrinsic factor is rare Lack of the intrinsic factor may occur when there is free gastric hydrochloric acid In typical addisonian pernicious anemia achlorhydria accompanies the essential defect but the intrinsic factor may be present with achlorhydria in other conditions or types of anemia It has been suggested that lack of intrinsic factor may be dependent upon gastritis arising from infections or toxic causes and that hereditary influences play a role Apparently the defect may rarely arise because of extrinsic destruction of the stomach mucosa by polyps or cancer or from gastrectomy Miller and Rhoads have produced a lack of gastric factor achlorhydria and macrocytic anemia in swine by a diet defective in vitamin B_2 (G) or a closely related substance The applicability of these observations to the etiology of macrocytic anemia arising from defective diet can scarcely be doubted but to ascertain how far dietary deficiency is operative originally in pernicious anemia requires further study

The thermostabile material in normal human and animal liver effective in pernicious anemia is soluble in 70 per cent alcohol in contrast to the material precipitated by 70 per cent alcohol which Whipple has shown is effective in hypochromic anemia due to blood loss The exact nature of the active principle which is nonprotein is unknown In addition to liver kidney brain and other tissues contain potent material which perhaps is different in character from that of liver In 1929 Sturgis and Isaacs showed that desiccated hog s stomach was as effective in pernicious anemia as liver Its effectiveness is dependent on the interaction of the intrinsic and extrinsic factors in gastric tissue The intrinsic factor in hog s stomach in contrast to the active principle of liver is readily destroyed by heat Because of the presence of extrinsic factor in liver extract and liver their potency may be enhanced some ten to twenty times by incubation with intrinsic factor

Pathology —The body usually shows no important loss of weight The skin and sclerae often possess a yellow tint The heart presents one of the finest examples of fatty tigering The tongue usually appears smooth and often red with absence in large part of the papillae There is atrophy both of the mucous membrane and underlying muscle With denudation of the epithelium vesicles may be present and sometimes shallow whitish ulcers Atrophy of the gastric mucosa with signs of inflammation is common The slightly enlarged liver has an

abundance of iron in the periphery of the lobules and in the Kupffer cells the pale centers of the lobules show fatty degeneration Free iron is found in other organs especially the lungs and spleen, and in the kidneys within the epithelium of the first convoluted tubules The spleen is usually enlarged but seldom double normal in size it may show myeloid formation which resembles in character the marrow of the bones Pigment metabolism is obviously abnormal and the blood plasma often contains increased amounts of pigment The van den Bergh reaction is an indirect positive Increased excretion of urobilin is a feature The accumulations of pigment and iron are rapidly utilized when specific treatment is begun

The red bone marrow is increased, soft and of deep red color There is a very great proliferation of primitive red cells often in sheets obliterating other structural details Only very few normoblasts can be found The white cell forming centers and megakaryocytes are fewer than normal Successive biopsies as Peabody has shown indicate that the marrow returns to normal in remissions Rhoads and his associates have suggested that in the presence of liver extract deficiency, aromatic compounds may increase the destruction of red cells which leads to anemia and that liver extract acts to detoxify injurious substances rather than to supply a building stone for the formation of blood However this may be within a few days following the administration of liver extract many primitive cells in the bone marrow have vanished and in their place normoblasts have appeared Their subsequent development into reticulocytes can account for the temporarily large increase of these cells in the peripheral blood

The characteristic lesion in the spinal cord is subacute combined degeneration a diffuse symmetric, marginal degeneration affecting the dorsal and lateral columns and usually first found in the upper thoracic and cervical portions There is early demyelinization often preceded by visible swelling of the myelin Later the axons degenerate The foci of degeneration (Lichtheim foci) usually appear first in the posterior columns later in the lateral columns and on each side of the anterior median fissure Glial proliferation is a relatively late phenomenon always incomplete and leaving a honeycombed appearance The dorsal roots may be affected early, and later the ventral roots Rarely similar degeneration occurs in the brain Peripheral nerve lesions are also found

Symptoms and Signs—Pernicious anemia as Addison wrote "makes its approach in so slow and insidious a manner, that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme This languor or weakness is often the first symptom of which the patient complains Other symptoms of anemia *per se* are of course common Digestive symptoms are the initial ones in about 30 per cent of cases and often may precede the anemia by years Burning and soreness of the tongue particularly of the anterior half is more apt to occur early than late in the course of the disease usually it is severe but for a few days at a time The red inflamed surface with vesicle formation leads to the smooth shiny atrophic tongue characteristic of the disease This condition may arise without any painful glossitis Sepsis commonly seen about the teeth may aggravate it The process may extend down the esophagus to the stomach All types of digestive symptoms may occur though indigestion does not necessarily coincide with a falling red cell count Distress from gas and mild intermittent diarrhea as well as constipation are common Gallbladder disease is frequent

Neural and rarely mental symptoms may be present long before there is clear cut evidence of macrocytic anemia Such symptoms appear first in at least one fourth of all cases This is particularly true of the older individuals In the natural course of the untreated disease symptoms referable to the neural system sooner or later develop in about 80 per cent of all cases and are not related to the degree of anemia Usually symptoms of neural involvement are confined to slight disorders of sensation persistent and usually symmetrical numbness and tingling of the hands and feet Among the earliest and commonest signs is diminution of vibration sense usually first detected in the lower legs Loss of the sense of position is apt to be manifest later All degrees of flaccid and spastic paralyses especially of the legs less often of the hands may be

seen Marked spastic ataxia indicates degeneration of the posterior and lateral columns of the spinal cord and occurs in about 10 per cent of all patients with nervous symptoms however the incidence of ataxia should decrease with early diagnosis and adequate therapy since proper therapy can prevent the development or progress of neural lesions When the posterior columns are involved ataxia absent reflexes and hypotonicity are prominent signs When the lateral columns are affected spasticity especially of the legs exaggerated reflexes hypertonicity and extensor reflexes occur In the advanced picture of combined sclerosis involvement of the sphincters of the bladder and rectum and contractions of the legs are prominent Stocking hyperesthesia or anesthesia may occur due to peripheral nerve involvement

Defects of the special senses can often be attributed to anemia *per se* Retinal hemorrhages are common but give little disturbance of vision The symptoms and signs referable to the circulation such as dyspnea are those common to anemia and may lead to a faulty diagnosis of cardiac disease Angina pectoris resulting from anemia may disappear as the blood becomes normal The blood pressure is usually low Impairment of renal function as measured by fixation of specific gravity is common when anemia is pronounced The disturbance subsides as anemia lessens The nonprotein nitrogen of the blood is seldom elevated above 50 mg Small amounts of albumin and casts are frequent in the urine and slight edema is common so that cases may be wrongly diagnosed as nephritis Encroachment on the myocardial reserve from anemia may lead to edema but it probably often results from low plasma proteins and changes in capillary permeability Pyelitis and cystitis are frequent complications especially in women

Fever usually irregular and of low grade is common in relapse The frequently described lemon yellow color of the skin and conjunctivae due particularly to bilirubinemia is by no means invariable Indeed the jaundice and pallor are usually not marked unless the red cells are below 2 000 000 per cubic millimeter Pigmentation on the exposed parts of the body and mucosae may be found Vitiligo often combined with brownish pigmentation, is not rare Although petechiae may appear anywhere especially beneath the tongue they are rarely numerous The spleen though slightly enlarged and palpable in about 40 per cent of patients who before the days of liver therapy had suffered relapses is now rarely palpable Likewise the liver was often moderately enlarged Such enlargements when due to the disease usually disappear with liver therapy *Relapses* and *remissions* of symptoms and anemia formerly such common and important features of the disease are now rarely observed except when therapy is omitted or the diagnosis unestablished for a long time

The Blood —The red cells are reduced to a greater extent than is the hemoglobin the difference giving rise to a high color index The total red count may be below 1 000 000 per cubic millimeter and is frequently below 2,500 000 when the patient is first seen and is feeling comparatively well The blood picture is typically that of a macrocytic anemia the mean corpuscular volume varies from about 110 to 160 cu microns Some increase in size of the cells is often observed before outspoken reduction in the total number of cells The mean corpuscular hemoglobin concentration is 32 per cent or more Many large oval deeply stained red cells usually macrocytes are a particular feature Microcytes also occur A graphic picture of the size of cells obtained from a Price-Jones curve shows typically a very abnormally wide distribution in diameter with a peak in the vicinity of 8.5 cu microns instead of as normally about 7 3 cu microns The common macrocytic picture may be modified by the presence of a complicating iron deficiency to a normocytic or mildly hypochromic type Poikilocytosis may be extreme Diffuse and punctate polychromatophilia is common but reticulocytes above 5 per cent are unusual in the untreated patient A variety of nucleated red cells may be seen normoblasts being the commonest Megaloblasts of Ehrlich are more commonly observed in pernicious anemia than in any other disease Primitive erythroblasts are rare

The white cells and particularly the platelets are usually diminished in number The

lymphocytes are apt to be relatively increased and the Arneth count of the polymorphonuclears shifted to the *right* Occasionally without known cause the eosinophils are moderately increased As *in normal individuals* they may reach over *50 per cent* after raw liver feeding but not after cooked liver or oral liver extract *therapy* As remission is inaugurated by adequate therapy, *particularly from red cell levels below 3 000 000* per cubic *millimeter there* occurs with regularity a temporary pronounced increase of reticulocytes (For details of this reaction see Lancet 2 319 1935) All the abnormalities *in the blood* including the increase of pigments vanish as the red cells and hemoglobin increase Achromia however may appear as the red cell count approaches normal

Diagnosis—The diagnosis of pernicious anemia is not to be based on the blood alone The history tuning fork and stomach tube are as *important instruments* for correct diagnosis as a well stained blood smear A diagnosis of pernicious anemia will rarely be in error if macrocytic anemia with slight icterus sore tongue achlorhydria and persistent paresthesias are present The typical blood picture is easily recognized but when the red count is but little reduced it is much more difficult to judge the significance of the findings A slight increase of mean corpuscular volume and a few large oval cells and microcytes is often suggestive A high color index and increased mean corpuscular volume however do not necessarily indicate pernicious anemia since other types of macrocytic anemia occur which are unrelated to pernicious anemia Furthermore the types of macrocytic *anemia mentioned* under etiology which are related to pernicious anemia may present an identical blood picture and many of the signs and symptoms of addisonian pernicious anemia The distinction from the latter types which cannot be described here is, however more a matter of nosologic than of physiologic moment Confusion must not be made however with the macrocytic anemia of leukemia with low white cell *count* and of the idiopathic aplastic' or refractory anemias A bone marrow biopsy may be helpful but of more value is a therapeutic test with liver extract given intramuscularly making observations on the course taken by the reticulocytes In the *chronic* aplastic anemias achlorhydria is only sometimes present *glossitis is at least* very rare signs of involvement of the neural system are absent, and the distribution curve of cell size is not so wide as in pernicious anemia in marked relapse The anemia of chronic nitrogen retention is sometimes macrocytic in character, the clinical and chemical findings should distinguish this condition Macrocytic anemia may occur *with cirrhosis of the* liver but there is rarely *great variability in the cell size as in* pernicious anemia The signs of hepatic disease are usually apparent Sometimes cirrhosis of the liver and pernicious anemia coexist The anemia of myxedema and the association of myxedema and pernicious anemia in the same patient and less often of diabetes may offer opportunity for diagnostic error The basal metabolism may be somewhat below or above normal in pernicious *anemia it tends to be low in* cases with neural lesions Other types of anemia such as occur in chronic hemolytic jaundice, may superficially resemble pernicious anemia Care must be taken to distinguish neural system symptoms from those due to multiple sclerosis and other disorders of the spinal cord

It is important to establish the diagnosis before the blood picture has been obscured by therapy If this is not done and if both liver and iron have been given it may become impossible to decide without omission of treatment whether or not liver therapy is necessary for the rest of the patient's life

Treatment—The fundamental principle *in the treatment of pernicious* anemia is the *continued* administration of adequate amounts of potent material for the given individual patient The object is not only to eradicate symptoms or place them under control but also to restore the patient's nutritional state to normal for the rest of his life The aim must be not only to return the hemoglobin and red cells to normal levels and keep them there but also to maintain a normal color index cell size *and cell* volume The amount of material necessary to accomplish this may be less than the amount needed to prevent the development or progress *not only* of neural lesions but

also of gastro intestinal disturbances The omission of treatment may not cause relapse for many months rarely for years but usually the individual will soon find that he is sick again and that often neural symptoms have developed or progressed quite unnecessarily Infections the presence of toxic substances increased metabolism arteriosclerosis or severe damage to vital organs may inhibit the action of liver extract and the presence of such complications often calls for a larger amount of material than would be necessary in patients without complications

source of active material for oral administration is provided by the combination of liver and gastric tissue No product should be employed unless objective proof of its effectiveness in known amounts is available Concentration of potency is achieved only with some loss of active material The United States Pharmacopoeia has defined for convenience a unit of liver extract as the amount of material which when given daily to patients with pernicious anemia has produced satisfactory hematopoietic response This amount is not necessarily effective in the control of neural manifestations

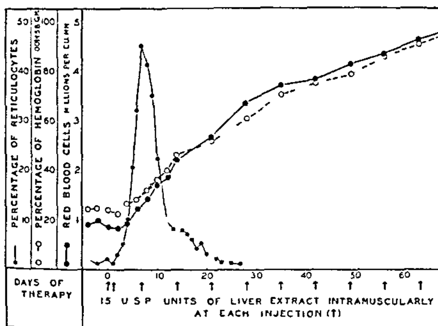


Fig 114—The response of the blood to liver extract in a case of pernicious anemia

Today it is not necessary for patients to eat 200 Gm of liver daily for concentrated preparations of liver and stomach are available and permit large amounts of potent material to be easily given Liver extract is at least sixty times as effective by injection as when given by mouth The parenteral route preferably intramuscular is the one of choice in sick individuals in those requiring large doses and in those with neural lesions The procedure is economical and gives assurance of sufficient material entering the body on selection of an appropriate dose If oral therapy is employed good results will be obtained with either stomach or liver preparations The most concentrated

tions A unit given daily in uncomplicated cases with an initial red blood cell level of about 1 500 000 per cubic millimeter or less will cause an increase of about 2,500 000 per cubic millimeter in a month

In discussing dosage it must be borne in mind that the amounts mentioned may be excessive in some cases and undoubtedly inadequate in others A severely anemic patient should be given intramuscularly 15 units of liver extract in 1 or more doses within six hours This implies a dose of *Liquor hepatis purificatus* (U S P XI) of from 1 to 15 cc derived from about 50 to 100 Gm of liver according to the preparation used This amount will usually suffice

to produce clinical remission If the case requires more than the usual amount of effective agent 5 units a day or 10 every other day for the next five to seven days is usually a wise procedure Thereafter, 10 units a week in single or divided doses is conservative At this stage orally administered material [*Extractum hepatis Liquor hepatis* or *Stomachus* (dried stomach) (U S P XI) or the stomach liver combination (Extralin) (N.N R)] can be substituted in doses of 1 unit a day The amount of liver extract will have been obtained from about 300 to 600 Gm of liver Many patients can be successfully treated by daily oral doses but the need of some patients is such that they cannot obtain enough by mouth

Effective treatment may produce subjective improvement within forty eight hours especially when liver extract is given in large doses by the parenteral route The patient first appears to be more alert to have more color and a better appetite By the end of two weeks he is much better fever if due to the disease, is gone and his blood is well on the way to normal with the plasma pigment normal Usually the lingual symptoms will have vanished the papillae of the tongue will have started to regenerate and the gastro intestinal symptoms will have greatly lessened On the contrary neural symptoms will rarely be altered at this time When the red cells reach 3 000 000 per cubic millimeter the patient can take up light exercise If achromia and other signs of iron deficiency develop which may be minimized by a diet rich in animal protein and iron daily oral doses of iron such as 15 grains (1 Gm) of ferrous sulfate should be given

In the course of two months from the beginning of treatment the patient usually attains a normal blood and the appearance of the tongue and the gastric mucosa is normal In spite of this achlorhydria almost always persists By now milder neurologic symptoms often have disappeared and more pronounced ones lessened The problem now arises as to proper dosage for continued therapy Unfortunately there is no way at present of knowing except by the method of trial and error Adequate treatment for pernicious anemia must never stop If neural symptoms are present the dose should not be decreased A dose of 10 units intramuscularly once in two weeks may be sufficient but, as practically all patients will have to continue to take some active principle, there is slight advantage in reducing the dose below a convenient level which has been found safe Too often one sees serious progress or development of neural lesions arising from too little potent material The failure of treatment implies an incorrect diagnosis inadequate dosage or strength of material or complications severe enough in themselves to be disastrous to the patient

The intramuscular injection of liver extract *may produce local pain and tenderness* rarely slight fever Allergy plays a role in some reactions It is wise therefore to employ at first a small dose which may be repeated in the same or larger amounts a few hours later, or as the circumstances suggest Intravenous injection demands attention to all the details required for this method of administering drugs

The treatment of pernicious anemia means more than the administration of substances to offset the deficiency The patient should be *in bed* while anemia is marked and the *diet* should be one optimal for health and containing a liberal amount of meat green vegetables and fruit The precise diet for each case will vary depending upon the desirability of the patient s gaining or losing weight the state of the digestion etc Rather often these patients do not tolerate fat well Occasionally *diluted hydrochloric acid* (U S P) in 2 to 4-cc doses may aid to minimize digestive symptoms but if these have not largely vanished within a month disease of the gallbladder should be suspected

Transfusion of blood is rarely indicated It should be performed if a very anemic patient at rest in bed shows signs of circulatory failure Sepsis and other complications must be attended to according to indications but if possible such procedures should be postponed until the red cells are near their normal level

It is of the utmost importance to give detailed attention to the results of neural involvement Suitable *physical therapy* meticulously carried out is invaluable Daily massage and passive motions should be given from the beginning and later on pro

cedures for retaining muscles are indicated Paresthesias often diminish as the red count increases above 3,500 000 per cubic millimeter and frequently disappear later Little change in the objective neurologic examination may be apparent then or subsequently but occasionally striking changes are observed Symptomatic improvement may be marked and is prone to occur to some degree in a large percentage of cases Patients originally unable to walk may become sufficiently improved to return to their occupation after several weeks or many months of treatment The sooner treatment is begun the better are the results Swelling of the myelin sheath ceases and further destruction of the axis-cylinders is prevented The treatment induces glial productivity Disorders due to peripheral nerve involvement can be expected to vanish relatively rapidly Every encouragement to practice walking and coordination without unduly fatiguing the patient should be given Indeed in practice every aspect of the patient as a human being and every factor in his case must be carefully attended to

Prevention —Prevention largely consists in the establishment of early diagnosis and adequate treatment A diet nicely adjusted with respect to all its constituents at an optimum will minimize the occurrence of certain cases *of macrocytic anemia Because* pernicious anemia may appear in families it is desirable for near relatives to be examined, scrutinizing particularly the state of their gastric secretion and blood from time to time in an effort to detect a latent case

Prognosis —The prognosis has been indicated above In well treated cases without complications it is excellent The properly treated patient loses all signs and symptoms of pernicious anemia except those caused by neurologic changes (which may retrogress) and those of achlorhydria and deficiency of the gastric intrinsic factor

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PURPURA

Definition —Purpura is a condition characterized by extravasations of blood into the skin and mucous membranes The areas of discoloration may vary from the size of a pinpoint (petechiae) to much larger areas known as ecchymoses

Occurrence —Purpura occurs as a symptom of many diseases and may be produced in various ways It is also a prominent feature of two distinct idiopathic conditions in which it is (1) associated with other exudative lesions joint and visceral symptoms and presents no recognized pathology of the blood (*idiopathic purpura*) and (2) characterized by paucity of the blood platelets and spontaneous hemorrhages from mucous membranes (*idiopathic thrombopenic* or *thrombocytopenic purpura* purpura hemorrhagica) A third less clearly defined idiopathic form of purpura is known as *purpura fulminans* There are also other rare idio

pathic and atypical conditions in which purpura may be a prominent symptom

Types.—*Symptomatic purpura* is usually *simple* and not dependent upon demonstrable disturbance of the blood nor associated with bleeding from the mucosae. It may result from mechanical causes, venous stasis, or from emboli as in endocarditis. It may appear in any infectious disease and constitutes the usual exanthem in some, notably epidemic cerebrospinal meningitis. Rashes, like those of scarlet fever and measles which are usually not purpuric, may be modified by the extravasation of blood into the skin when the infection is severe. The hemorrhages may be seen in nutritional disorders, in many toxic states including those resulting from the administration of drugs (as copaiba, iodides, quinine, atropine, etc.), and in cachectic patients, in chronic nephritis, endocrine disorders, disease of the liver and occasionally in diseases entailing degenerative lesions of the spinal cord.

Symptomatic Purpura with Blood Defects.—Purpura may be symptomatic of an abnormality of blood coagulation, as for example in prolonged jaundice, severe liver disease, *erythremia* and *some forms of* sepsis. When associated with a marked reduction of platelets in a recognized disease it is known as *symptomatic thrombopenic* or *thrombocytopenic purpura*.

Symptomatic Thrombopenic or Thrombocytopenic Purpura (Purpura Hemorrhagica).—This is associated with bleeding *from the mucosae as in the idiopathic condi*tion. The decrease in the number of platelets can be brought about by:

(1) Destruction or depression of the activity of their parent cells, the megakaryocytes of the bone marrow, such as occurs in aplastic anemia which may be idiopathic or result from benzol poisoning, arsphenamine, bacterial toxins or excessive irradiation with roentgen rays and the like.

(2) Displacement of megakaryocytes by abnormal cells as in the leukemias, metastatic tumors and other conditions.

(3) Destruction of platelets or their removal *from* the circulation as for example in poisoning from some drugs and in certain allergic and toxic states.

Idiopathic Purpura (*Primary or Anaphylactoid Purpura*).—*Definition*.—A frequently recurrent but rarely fatal morbid state, characterized by purpura and often associated with other exudative lesions, joint manifestations and visceral symptoms but without known abnormality of the blood.

History.—Schönlein described cases with joint manifestations and Henoch those with intestinal crises. Osler clearly showed that the type with purpura, erythema and allied skin conditions especially with visceral disturbances may be considered essentially a clinical entity with protean manifestations.

Etiology.—Children and young adults are usually affected but no age, sex, or race is exempt. The cause of the condition is unknown. Infection probably accounts for some cases, others because of their resemblance to serum sickness and because sensitization to a specific protein or to certain food is *sometimes demonstrable are apparently* manifestations of allergy. Hypersensitivity to cold may be a cause.

Purpura simplex may be hereditary and familial and is more common in women than men, occurring in later generations at progressively earlier ages. Rheumatic fever, arthritis and fibrositis is common in this group.

Morbid Physiology.—The permeability of the small blood vessels is altered and mechanical factors probably influence the distribution of the lesions. The manifold lesions may be explained by the extravasation of varying proportions of plasma and formed elements of the blood and by local vascular changes. Every lesion, internal or external—purpura, erythema or edema according to the blood elements that permeate the vessel walls—is to be *considered focal*.

The *blood* undergoes no constant change. Anemia may be present and the white count is sometimes slightly elevated. The platelet count is not low and the clotting time is essentially normal.

Symptoms and Course.—Idiopathic purpura is divided artificially into various types *according to the anatomic* distribution of the lesions. Patients may exhibit purpura only (purpura simplex) or there may be concomitant articular symptoms (Schonlein's disease, purpura rheumatica). Some develop symptoms attributable to visceral lesions, those of the intestines causing crises of abdominal pain (Henoch's purpura). Various

combinations of skin joint, and visceral lesions are seen The patient may exhibit at one time purpura alone at another, urticaria or erythema while visceral symptoms may develop with or without skin manifestations Those who exhibit purpura alone are usually free from significant constitutional disturbance The eruption may be local or general one group or more of lesions appearing during the course of several days The lesions then usually subside but may recur at intervals of weeks or even years In others an attack of the disease begins with fever malaise and a sore throat which are followed shortly by polyarticular pains Days or even weeks later perhaps after all initial symptoms have subsided an eruption may appear which is often purpuric and commonly associated with urticaria and erythema Edema is variable in degree The arthritic and cutaneous lesions usually subside in a few days but often recur together or independently at intervals of one to six weeks

The extravasation of plasma and cells into some viscus may take place whenever there are exudative skin lesions or arthritis not only in close association with the appearance of such symptoms but often when they are absent They are rarely found elsewhere than in the intestines or kidneys Fever and malaise generally precede the localizing symptoms Foci of hemorrhage and edema in the gastro intestinal tract give rise to crises of pain which is often colicky to diarrhea melena and even to intussusception Similar infiltration in the kidney may result in hematuria escape of albumin and depression of renal function and thus simulate acute nephritis Uremic symptoms are exceedingly rare Severe visceral disturbances seldom last more than a few days although like arthritis they often dominate the picture Their intensity fluctuates Recurrent attacks sometimes ensue for many years

Complications are infrequent Endocarditis has been reported to occur Enlargement of the spleen frequently develops in children who have had repeated attacks of the disease but is uncommon in adults

Diagnosis —In the presence of purpura or exudative skin lesions and when the platelet count is normal the diagnosis is usually simple If purpura is associated with urticaria erythema or edema it is apt to be of this idiopathic variety Diseases of which purpura may be a symptom must be excluded as well as *thrombopenic purpura*

The articular pains may suggest *rheumatic fever* but purpura itself is rare in this condition *Scurvy* is readily differentiated by careful examination of the dietary history and administration of antiscorbutic substances

The cases most difficult to diagnose are those in which visceral symptoms develop without skin lesions The crises of pain so closely resemble those of certain acute abdominal conditions that operation cannot always be forestalled Operation causes no abnormal hemorrhage because the elements associated with the coagulation of the blood are essentially normal Symptoms referable to the genito urinary tract often lead to a diagnosis of *acute nephritis* and in the absence of skin lesions this cannot be, positively ruled out In every child with severe abdominal pain or hematuria the possibility of idiopathic purpura must be considered and the skin examined for exudative lesions

Prognosis —The outlook as to life is nearly always excellent Individual attacks last ordinarily from one to six weeks while recurrence at intervals of months or years is not unusual As the individual grows older the disease tends to become milder or to disappear

Treatment —There is no specific treatment for the disease In an effort to alter favorably the endothelial permeability many substances have been advocated but none produces a cure Symptoms must be treated as they arise and good hygiene instituted If the ingestion of particular food stuffs causes symptoms they should be excluded from the diet and if the patient is unduly sensitive to some protein adequate desensitization may be attempted

Idiopathic Thrombopenic (Thrombocytopenic) Purpura (*Idiopathic Purpura Hemorrhagica Morbus Maculosus of Werlhof Pseudohemophilia*) —*Definition* —Idiopathic thrombopenic purpura is a disease that may be acute or chronic and is characterized by a marked and unaccountable diminution in the number of blood platelets spontaneous hemorrhages from mucous membranes and purpura

History.—Werlhof in 1731 first differentiated the condition from other varieties of hemorrhagic disease In 1887 Denys noted the platelet reduction Hayem and Bensaude and Rivet called attention to the chronic type of the disease and Kaznelson in 1916 showed the striking results that follow splenectomy

Etiology and Morbid Physiology.—The cause is obscure Females are affected more often than males Young individuals are more often afflicted than older ones Acute cases suggest an allergic state The chronic form is sometimes congenital or familial and may be of quite a different nature from the acute Postmortem examination has revealed no characteristic lesions Signs of extensive capillary hemorrhage are the outstanding feature and are associated with a diminution of platelets but there may be other unknown factors causing the increased capillary permeability Probably two conditions exist that may be called idiopathic thrombopenic purpura one where the megakaryocytes are decreased and which represents an aregenerative type of bone marrow disease and second a condition where there is no abnormality of these cells The latter may be considered more truly idiopathic or essential thrombopenic purpura Cases are also recorded with morphologic variation in the megakaryocytes

Experiments have shown that injection of the serum of rabbits immunized against the platelets of the guinea pig causes destruction of normal guinea pig platelets Moreover guinea pigs which have received inoculations of antiplatelet serum, rapidly develop all the features of clinical thrombopenic purpura These animals megakaryocytes are normal An allergic state as a cause of thrombopenic purpura is supported by its provocation by 'sedormid' nirvanol arsphenamine gold quinine and other drugs by food sensitization and by its occurrence one to three weeks after subsidence of an acute infection Some cases are associated with focal infection and rarely, with tuberculosis—conditions which aggravate chronic cases Endocrine disorders are suspected in some cases and rarely dietary deficiency may play a role Causative agents should be sought but in many cases the etiology of thrombopenic purpura remains unknown

Clinical experience indicates the importance of a capillary defect in the etiology of purpura hemorrhagica Bedson and Roskam s experimental studies show that both thrombopenia and altered vascular reactivity play a role Macfarlane has seen normal capillaries contract after injury, but when the bleeding time is prolonged, contraction is greatly decreased

Hemorrhage in purpura hemorrhagica is not always closely related to the degree of thrombopenia The circulating blood platelets are often large and abnormally granular They may be absent or as is usual present in numbers below 100 000 per cubic millimeter Bleeding usually ceases when they are above this number The bleeding time is prolonged sometimes for hours The coagulation time is rarely more than slightly prolonged but because of the paucity of platelets the loosely woven clot does not retract The degree of anemia is particularly dependent on loss of blood but defective blood formation also may be influential The red and white blood cell picture is usually similar to that seen after mechanical chronic loss of blood but if cases with signs of an aregenerative marrow are considered idiopathic purpura hemorrhagica then leukopenia and all signs of marrow depression may supervene In acute cases immature bone marrow cells that cannot be accounted for by blood loss may appear in the circulation Lymphocytosis without leukopenia may be pronounced

Symptoms.—*Spontaneous capillary bleeding* from and into mucous membranes is the clinical feature that distinguishes thrombopenic purpura from most other forms The bleeding may occur into any tissue It varies from slight oozing from a single source to profuse bleeding from many sources Hemorrhage from the mucosae of the nose and mouth is particularly common and that from the uterus and into the retina frequent The cutaneous hemorrhages may be extensive but more often consist of but a few petechiae and are rarely associated with other exudative lesions The vulnerability of the capillaries permits slight trauma to produce ecchymoses

Fever is common in the more acute and severe cases The spleen may be moderately enlarged particularly in the chronic type but abnormally small spleens are also re-

corded No other symptoms or signs occur except those attributable to hemorrhages or anemia

An acute and a chronic form of the disease are recognized

In the *acute type* the hemorrhages often begin abruptly without warning or after some days of debility In favorable cases the symptoms usually disappear within three weeks as inexplicably as they arose In others the course may be short and fatal The hemorrhages may persist for days and then cease only to recur after an interval of days or weeks and may thus render the disease *intermittent* for many months Such subacute conditions may become chronic and patients may live for years without much severe bleeding Other patients suffer more or less severe bleeding *continually* for weeks or months and become gradually exsanguinated or die from a cerebral hemorrhage or the like

The chronic type of the disease does not usually develop from the acute form At the time of a brisk hemorrhage the patient often states that for years he has bruised and bled easily, but not severely and often has had petechiae The platelet count usually remains below normal so that the patient continually shows some signs of hemorrhage The hemorrhages however may be so slight that for many years the individual gives little thought to the lesions More profound ones may occur intermittently particularly from the nose and vagina Rarely the number of platelets fluctuates markedly from well above to much below normal so that symptoms may be truly intermittent A pronounced drop in the platelets may occur only in association with menstrual periods

Diagnosis —Spontaneous hemorrhage from a mucous membrane and a paucity of platelets are sufficient evidence for a diagnosis of thrombopenic purpura and differentiate it from hemophilia The idiopathic disease is to be diagnosed after excluding a cause or conditions in which thrombopenia is a symptom *Aplastic anemia* is to be distinguished particularly by rather persistent leukopenia Bone marrow biopsy may be required to exclude myelosclerosis *Acute leukemia* even when in a nonleukemic phase seldom will be confused if a proper blood examination is carefully interpreted Rarely acute thrombopenic purpura occurs with blood pictures suggesting leukemia or infectious mononucleosis which does not necessarily herald fatality

The joint symptoms varying exudative skin lesions and visceral crises common to idiopathic purpura are rare in the thrombopenic forms while the characteristic blood pathology of the latter further serves to distinguish these two conditions *Hemorrhage from telangiectases easy bruising without spontaneous purpura* particularly in women and other hemorrhagic syndromes need cause no confusion as in these conditions there is no paucity of platelets The blood platelets are rarely involved in scurvy which presents quite a different symptomatology Their decrease however may occur in some individuals with a deficiency of vitamin C

Chronic cases of rare types of hemorrhagic disease are reported with increasing frequency Some cases such as *hereditary hemorrhagic thrombasthenia* (Glanzmann 1918) and *constitutional thrombopathy* (von Willebrand 1926) are hereditary appearing in both male and females These two conditions probably represent one disease entity In both the bleeding time is prolonged without alteration of the coagulation time or paucity of platelets The clot retracts except in some cases considered thrombasthenia The abnormal bleeding time may appear only intermittently The spleen is rarely enlarged Sporadic cases of this sort have been reported There also occur atypical hemorrhagic conditions without detectable blood abnormality instances of which may be associated with altered ovarian function These rare conditions should be distinguished from classic chronic thrombopenic purpura

Prognosis —Spontaneous recovery is not rare in acute cases If a given attack does not show signs of abatement within a few weeks an unfavorable outcome is probable but death or less often recovery may be delayed many months

The chronic type shows less tendency to permanent recovery than the acute The disease may last a lifetime but the condition tends to become gradually worse The above statements apply particularly to nonsplenectomized cases

Treatment —Any possible exciting agents such as drugs, should be removed and undesirable conditions such as hypersensitive states *should be alleviated* Cure may result following removal of an infectious process so that focal sepsis must be treated appropriately Surgery, however, except for splenectomy, should be undertaken cautiously when the blood platelets are few Iron and foods that enhance blood regeneration may aid in lessening anemia Sometimes, in subacute cases, the daily ingestion of large amounts of whole liver has been associated with rapid improvement Patients should follow a nutritious diet and avoid fatigue

Splenectomy because of its recognized influence in allowing the blood platelets to increase in the circulation and its possible effect in decreasing their abnormal destruction and enhancing capillary closure, has been shown to have a strikingly beneficial effect in *chronic* essential thrombopenic purpura but rarely in chronic cases with purpura hemorrhagica where the bone marrow is implicated The operation leads to symptomatic cure in about 70 per cent of cases In 30 per cent there is obvious improvement but episodes of mild bleeding recur Rarely there is no benefit sometimes because of existing liver disease or complications The operative mortality is slight The blood platelets usually increase in number very rapidly after removal of the spleen and are abnormally abundant After about a week the platelet count falls to remain usually for at least many months near the normal level The number of platelets tends, however to be low and in some patients they again become sparse The bleeding time may be more favorably affected than the number of platelets This suggests that removal of the spleen may favorably effect capillary closure There are splenectomized patients with few platelets who do not have serious hemorrhage They may give birth to children with very few platelets who bleed very little or not at all and who after some weeks have a normal number of platelets Great variation has been reported concerning the recovery of retractability of the blood clot The increased number of blood platelets appears to be only one factor in the arrest of the purpuric manifestations Exactly how extirpation of the spleen achieves at least temporary cure and the arrest of gross hemorrhage is not understood

If chronic purpura hemorrhagica is sufficiently disabling, splenectomy is indicated but this operation is not advised for the acute case If, however the acute case progresses or become subacute and of a few months duration, splenectomy may be desirable The postoperative mortality is considerably greater in acute than in chronic cases Splenectomy is, of course contraindicated in *symptomatic thrombopenia*, and it is wiser not to attempt the operation when the diagnosis is doubtful Each case must be considered individually One must not act hastily and should recall that many patients with the chronic form live for years with relatively insignificant symptoms and that spontaneous improvement may occur

Irradiation of the spleen or the body as a whole with roentgen rays sometimes increases blood platelets in essential thrombopenia but its effects are apt to be temporary Perhaps parenteral vitamin C therapy affects certain cases favorably but if so deficiency of cevitamic acid (scurvy) is probably the underlying defect

The most important method of checking hemorrhage is blood transfusion This may be resorted to when the bleeding or anemia is severe Transfusion of an adequate amount of blood relieves anemia and usually causes cessation of bleeding for from three to six days To control hemorrhage transfusion of 100 to 300 cc of blood at frequent intervals is more desirable than isolated large transfusions and although the platelets may be little altered the bleeding time is brought under control Repeated transfusions occasionally appear to have some unexplained specific effect but they often tide the patient over until his own platelets in the peripheral blood become normal Antivenin and snake venom have a hemostatic effect in some cases

Purpura fulminans, first described by Guillot is extremely rare The etiology is unknown It occurs chiefly in children and is characterized by very large symmetric ecchymoses on the skin The onset is sudden with high fever and death is usual within

a few days The platelet count is reported as normal and hemorrhage from mucous membranes is not a feature

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HEMORRHAGIC DISEASE OF THE NEWBORN

(*Melena Neonatorum*)

Definition—Hemorrhagic disease of the newborn is a self limited disturbance occurring only in the newborn and characterized by spontaneous hemorrhages which may occur in any tissue of the body There is an exceedingly low prothrombin concentration in the blood as determined by the methods of Quick and Warner Brinkhaus and Smith and cure is prompt by the oral and parenteral administration of vitamin K

History—The disease was first adequately described by F Minot in 1852 In 1908 Lambert demonstrated the therapeutic effectiveness of injection of human blood while later J E Welch (1910) and Schloss and Commisky (1912) added further data to our knowledge The new knowledge concerning vitamin K has been added by various investigators since 1937

Etiology and Morbid Anatomy—The disease occurs in about 1 per cent of all newborn infants It is not recurrent and is usually manifest before the fourth day of life and does not develop after the tenth

The prothrombin concentration of the blood normally drops abruptly during the first few days of life but is soon restored spontaneously The recovery is probably brought about by the establishment of a bacterial flora in the intestines which can initiate the synthesis of vitamin K so that it becomes available to the infant for the production prothrombin A delay in restoration of the prothrombin of the blood occurs

in hemorrhagic disease of the newborn, with the result that the prothrombin content is exceedingly low The coagulation time of the blood is usually prolonged, the clot retractile, and the platelets present in at least normal numbers The bleeding time is rarely abnormal Except for extravasation of blood and the results of hemorrhage, postmortem examination is negative

Symptoms—Failure to nurse fretfulness subnormal temperature and even prostration may precede the hemorrhage Jaundice is often present The spontaneous bleeding causes ecchymoses which may be the only sign of loss of blood Bleeding often takes place from the umbilical stump and intestines Hematomata and bleeding from instrumental abrasions are common Less frequently there is intracranial hemorrhage or bleeding from serous surfaces kidneys or vagina The loss of blood from a single source may be slight but the total amount lost may be sufficient to produce symptoms of marked anemia

Diagnosis—In many cases of intracranial hemorrhage in babies following delivery it seems likely that the lowered prothrombin is a factor but trauma alone is probably the chief cause *Congenital fibrinogenopenia* which may cause bleeding is very rare At this age *melena due to ulcer* is seldom seen The usual forms of *idiopathic purpura* are very rare in infants but the *purpura and hemorrhages of syphilis or pyogenic infections though rare must be differentiated* from the manifestations of hemorrhagic disease of the newborn The hemophilic baby rarely bleeds during the first few weeks of life and melena a feature of hemorrhagic disease of the newborn is rare in hemophilia

Prognosis—The outlook for untreated infants is grave over 50 per cent die within a few days When human blood is injected early the prognosis is vastly better Treatment with vitamin K cures the condition promptly Once the manifestations of the disease have disappeared there is no recurrence

Treatment—The synthetic product 2 methyl 1 4 naphthoquinone may be given orally in fat soluble form or parenterally as a water soluble preparation for a few days An average daily dose is 0 75 mg, intramuscularly, or 3 mg of fat soluble material orally which requires good absorption Within eight hours the prothrombin time is shortened and bleeding ceases If the mother receives before delivery 1 to 2 mg intramuscularly for each of 2 days the infant s prothrombin time will remain normal There are many other synthetic and natural preparations with varying potency that are effective

Unless the hemorrhage is severe a blood transfusion (80 cc) need not be given Other treatment is symptomatic and depends on the needs of the individual case

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HEMOPHILIA

Definition—Hemophilia is an hereditary disease in which the coagulation time of the blood is much prolonged The disease occurs practically only in the male but is transmitted only by the female A marked tendency to hemorrhage throughout life is characteristic Bleeding sometimes occurs spontaneously but usually follows trauma even when the injury is trifling

History—There are passages in the Talmud which indicate that the ancient Jews knew of the disease Consbrush in 1793 and Rave in 1796 described a case It was J C Otto of Philadelphia who brought attention to the condition by his excellent descriptions published in 1803 and 1805 Bulloch and Fildes monograph is a classic

Incidence and Etiology—The etiology of hemophilia is a mystery The disorder once

started is transmitted to males from generation to generation through the female Hemophilia is apparently a recessive sex character linked to a single male chromosome Its incidence follows the laws of mendelian inheritance The female conductor transmits the condition to about two thirds of her male offspring while about one third of the female offspring are not conductors Cases reported in females are usually proved unauthentic If a male hemophilic should marry a woman capable of transmitting the disease it would be possible for their female children to be hemophilic The fecundity of the females of bleeder families is peculiarly great, and among their offspring there is a predominance of males who never transmit the disease The children of hemophilic fathers are more often female than males

Morbid Anatomy —Custer and Krumbhaar have noted that the megakaryoblasts and megakaryocytes in the bone marrow may be markedly increased Postmortem examination otherwise shows that the organs are normal except for the results of hemorrhage

The Blood—The numerical counts of the formed elements are normal except after hemorrhage The number of blood platelets is never diminished The delay in coagulation time is typical but varies from time to time in the same case The cause of the delay in coagulation time has been the subject of much study and the multiplicity of terms used in discussing the problem has caused confusion It is evident however that there is a fundamental alteration in the physical chemistry of the coagulation factors this has been described as a shortage or qualitative defect of prothrombin an increase in the quantity of antiprothrombin changes in calcium ionization etc A qualitative defect of the platelets or their slow disintegration has also been considered of significance A defect in some factor of platelet free plasma however, must be considered to exist This is associated with the globulin f action of the blood and there may be a deficiency of plasma thromboplastin The blood may manifest the reclotting phenomenon but the clot once formed retracts normally

Symptoms —The essential symptom of hemophilia is hemorrhage following trauma which would not normally cause bleeding The injury may be very trivial spontaneous hemorrhage is rare The bleeding which often lasts many hours and sometimes days tends to be of a persistent oozing nature, and may lead to profound anemia or be fatal though death rarely results from the first loss of blood The condition usually becomes evident in early childhood but may not be apparent until later The tendency to bleed and the degree of bleeding vary in the same and different individuals The hemorrhage may be external internal or into joints Although pin pricks do not cause bleeding scratches may initiate serious hemorrhage Thus the veins and ears may be punctured with impunity indicating that the bleeding time is normal Obstinate epistaxis is frequent The cutaneous lesions are in the nature of bruises that is they are hematomata not purpuric spots Hemorrhages into and about joints are common and may do no lasting harm but they usually cause destruction of bone and lead to changes similar to those occurring in hypertrophic (degenerative) arthritis Internal hemorrhages including those into the muscles and joints may cause pain and fever

Diagnosis —Obstinate hemorrhage is more often due to local injury or disease than to abnormalities of the blood and the mere fact that bleeding persists does not justify a diagnosis of hemophilia The diagnosis depends on the family history the occurrence of repeated bleeding—usually protracted and from more than one location—joint manifestations and the coagulation time of the blood Mild atypical or sporadic cases are rare and may not be suspected until some accident or operation takes place

Hemophilia is to be sharply differentiated from *purpura hemorrhagica* especially from the chronic idiopathic form This latter disease occurs in either sex and is rarely congenital or familial but it may appear in hemophilic families The condition of the blood in these two diseases is very different In hemophilia the platelets are present in at least normal numbers the bleeding time is normal and the clot retracts in purpura hemorrhagica the number of platelets is much decreased the bleeding time is prolonged and the clot is nonretractile and

soft In the latter condition, the coagulation time is usually not far from normal instead of being prolonged as in hemophilia Purpuric skin lesions and truly spontaneous bleeding are evidences of purpura hemorrhagica, and not of hemophilia Rare cases of atypical and familial hemorrhagic disease exist, such as the hereditary thrombasthenia of Glanzmann and the constitutional thrombopathy of vonWillebrand Such conditions are to be distinguished from hemophilia

Hemorrhagic disease of the newborn is neither familial nor recurrent and develops only in the first few days of life—a time when the male hemophilic baby seldom bleeds *Melena* is rare in hemophilia The blood in *hereditary hemorrhagic telangiectasia* is normal and this condition as well as *scurvy* is readily distinguished from hemophilia

Prolongation of the coagulation time is not pathognomonic of hemophilia but occurs also in sepsis nephritis liver disease and jaundice among other abnormal states It is rarely as marked in these conditions however, as in hemophilia

Prognosis —Hemophilia tends to be fatal before the subject attains adult life Few patients reach adult life without suffering some disabling deformity of the joints If the manifestations are mild the condition will probably not become worse The tendency to bleed however, often varies greatly so as to suggest remissions and relapses of weeks to years in duration

Treatment —The *prevention* of hemophilia is a problem of eugenics The *course of the disease* cannot be fundamentally altered Hemophilic individuals and male children of tainted stock must be guarded from traumatism and must know of a suitable blood donor in case transfusion is necessary General principles of hygiene and nutrition should be carefully followed The *joints* should receive treatment similar to that for chronic arthritis in order to prevent deformity

The use of tissue protein extracts from the human placenta as described by Eley Green and McKhann is of some value particularly in children There is increasing evidence that ovarian and estrogenic substances have no important value

In case of hemorrhage the patient must have absolute quiet Morphine may be necessary The blood of hemophilic patients eventually clots and the hemorrhage tends to stop spontaneously, consequently treatment varies according to the severity and location of the bleeding The local application of thromboplastic or thrombic material may be of great value so that the patient should keep at hand such material for local use Rabbit thrombin is especially valuable as a local hemostatic It should be applied dry and kept in place by a firm dressing or pack It is rapidly effective and very serviceable when teeth are removed The desirability of transfusion varies in each case When loss of blood threatens life transfusion of enough blood (usually 800 cc) to restore the coagulation time and the plasma volume to approximately normal is necessary The effect of transfusion on the abnormal clotting mechanism and thus on the disease is only temporary, yet it is of great value in checking hemorrhage About four days after transfusion, the clotting time of the patient's blood returns to that before transfusion Small amounts of blood 25 to 100 cc can affect the coagulation time as much as large amounts (500 cc), but probably the clinical effect of large amounts on the cessation of bleeding is more dramatic and longer lasting However a single injection of a small amount is often effective and repeated every six to forty eight hours can check and prevent blood loss Hemophilics can undergo a surgical operation without serious hemorrhage if blood transfusions are appropriately used to hold the coagulation time near normal during operation and while the wound is healing

Sensitization to foreign protein offers a means of treating hemorrhage The patient can be sensitized to such a *substance* as sheep serum which requires about ten days Thereafter upon receiving *intradermally* a small amount of the same substance the coagulation time of capillary *blood* but seldom venous blood is temporarily decreased

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ERYTHREMIA

(*Polycythemia [Rubra] Vera Splenomegalic Polycythemia Vaquez's Disease Osler's Disease*)

Definition—Erythremia is a chronic slowly progressive eventually fatal disease of unknown origin characterized by excessive erythroblastic activity of the bone marrow which induces a persistent polycythemia and splenomegaly The increase of erythrocytes usually leads to a red cyanotic appearance of the skin an erythrosis (Lundsgaard) an increase in the viscosity and in the total volume of the blood and distention and engorgement of capillary vessels

History—Vaquez in 1892 described a case but general knowledge of erythremia remained lacking until Osler drew attention to it in 1903

Incidence—Erythremia is rare It occurs in all races but especially in Jews born in eastern Europe It particularly occurs in individuals about fifty years old Some cases are familial The blood of members of the patient's family may contain an abnormally large number of red blood cells while the individuals remain free from symptoms

Etiology—The eventual level of the red cell count is controlled by the oxygen tension of the bone marrow, but a general anoxemia apparently is not operative in erythremia A localized anoxemia in the bone marrow may play a role Excessive gastric secretion cannot be considered seriously as a cause of erythremia because if this were the case polycythemia could be induced in any normal individual by continued administration of liver or stomach preparations such material however does not act in this way

Morbid Anatomy—There is a striking increase in the quantity of active red bone marrow which replaces the normal yellow marrow The microscope permits demonstration of hyperplasia of not only the red cells but also the white cells and megakaryocytes In the bone marrow vascular changes of a fibrotic nature are recorded by Reznikoff Foot and Bethea which are distinct from the medial fibrosis of general arterio or arteriolar sclerosis The basal metabolism is often high when the formation of blood is augmented Extramedullary formation of blood is unusual Actual myeloid transformation of the spleen and other organs may occur The splenic enlargement is usually caused by hyperplasia of the pulp and distention with blood Anemic infarcts are common and thrombosis is not rare a fact which may lead to such a condition as perforation of the stomach Peptic ulcer occurs in about 8 per cent of the cases Extreme vascular engorgement of all organs is characteristic The increased blood volume the physical character of the blood and the impeded circulation may lead to degenerative changes in the vascular system On the contrary changes in the vascular system of the bone marrow may be primary and lead to compensatory erythrogenesis and thus increased viscosity and impeded circulation

*The Blood**—The total volume of the blood in typical cases is much increased that of the plasma only slightly The hematocrit reading is important Haden has

* A colored plate of the blood of erythremia is shown in the Am J M Sc 166 469 1923

shown that the red cell mass per kilogram of body weight is constantly high in erythremia and not significantly changed in symptomatic polycythemia The red cell count bears no direct relationship to the blood volume The proportion of cells to plasma may be greatly increased This causes an increased viscosity so that grossly the blood, which is abnormally dark red appears thick and sticky and the corpuscles settle in the plasma very slowly This physical condition of the blood may delay coagulation and favor nonretractility of the clot

As a rule, the hemoglobin ranges between 20 and 40 per cent above normal As the need of the body is no greater than normal the venous blood is abnormally rich in oxygen The red cell count is usually 7 000 000 to 11 000 000 per cubic millimeter The color index is low sometimes strikingly so and achromia may consequently be marked The red cell count and amount of hemoglobin may vary considerably from time to time not only because of local conditions but also because of fluctuations in production and perhaps in destruction Anerythremic phases occur and anemia may develop when myeloid metaplasia is present

The abnormal activity of the marrow is reflected in the peripheral blood by the presence of abnormal and increased numbers of immature red cells bone marrow leukocytes and often platelets The abnormality of the red cells frequently consists in only a slight variation in size and the appearance of an occasional polychromatophilic cell Unevenness in the depth to which the cells stain is a feature The white cell count is often 15 000 per cubic millimeter sometimes much higher The blood may resemble that of myelogenous leukemia and polycythemia may rarely occur in leukemia (erythroleukemia) There may be an increased output of urobilin, microcytosis and certain alterations of the plasma and the red cell fragility which suggest that the increased destruction of blood is compensatory

Symptoms *—The *onset* of erythremia is insidious The symptoms which are largely directly referable to polycythemia often do not appear until engorgement has taken place in even the smallest vessels Some symptoms are attributable to increased metabolism Lassitude, increased sweating loss of weight headache vertigo tinnitus surging and congestive sensations dyspnea and various gastro intestinal symptoms sometimes associated with gastric achylia, are common The typical red cyanosis most obvious in the face and ears may be the patient s first complaint The peculiar color may be absent and the polycythemic patient may even be pale Changes in position external temperature and mood often cause striking fluctuations in color The vascular distention and engorgement is also shown in the capillaries of the nail fold by the bluish red color of the tongue and by congestion of the mucosae conjunctivae and retinae Irritability depression and forgetfulness are common Slight palsies of cranial nerves are not unusual Hemorrhages from or into any part are common so that apoplectic seizures are not rare The enlarged spleen often reaches to the umbilicus and may be associated with a dragging sensation as well as pain The liver is often increased in size and sometimes cirrhotic Neuralgia like pain in the extremities and muscular spasms are sometimes striking Swelling of joints is rare Cardiac failure may be manifest The heart is often not enlarged although slight hypertrophy and some increase in rate is not unusual The blood pressure is sometimes elevated Kidney function may be impaired usually temporarily by engorgement infarction or hemorrhage Pulmonary emphysema arterial degeneration and its varying results erythromelalgia and pigmentation of the skin sometimes occur

There are atypical cases of erythremia some of which are congenital and some of which begin in early life A benign familial form occurs Erythremia in elderly patients with high blood pressure usually with renal disease but without splenic enlargement has been described by Gaisbock and Hess Polycythemia of this type seems to be secondary

Diagnosis —The diagnosis depends upon the recognition of a persistent absolute polycythemia for which there is no obvious cause The appearance of the patient and

* A colored picture of a patient with this disease is shown in Fig 29 in Bedside Hematology by Gordon R Ward 1914 W B Saunders Co and in the 1939 Year Book of General Medicine p 328 The Year Book Publishers Inc Chicago

the splenomegaly should render diagnosis simple The *erythrocytosis* or *secondary polycythemia* which occurs with circulatory stasis from chronic cardiac disease—particularly congenital—and chronic pulmonary disease (emphysema) must not lead to confusion The cyanosis characteristic of these states as well as that due to methemoglobin and CO hemoglobin should be distinguished from the erythrosis of erythremia The saturation of the arterial blood with oxygen in polycythemia due to cardiac or pulmonary disease is less than in erythremia Confusion must not arise from the relatively slight increase of red cells that result from numerous causes such as residence at high altitude and from the administration of certain drugs exposure to some poisons and marked vasomotor instability

The gastro intestinal symptoms and those referable to the central nervous system heart kidneys and special sense organs may lead to an incorrect diagnosis of local primary disease

Prognosis —The course of the disease is chronic and there are spontaneous and prolonged remissions and exacerbations which necessitate a certain reserve in considering the results of therapy It is eventually fatal though death is often produced by other causes After the development of definite symptoms the *duration of life is seldom less than four years* Some patients live twice as long and others for even twenty years or more Death may occur during a sudden exacerbation or as the result of vascular complications *especially* thrombosis or hemorrhage Adequate treatment by modern methods permits a more favorable prognosis

Treatment —*The patient must lead a life* that does not cause intensification of symptoms He should avoid mental and physical strain extremes of temperature and over eating

Venesection relieves rapidly such symptoms as headache Its repeated use is an excellent form of treatment decreasing the red cell mass and reducing the color index The hematocrit level is an important guide to treatment The red cell level may become very high and the hemoglobin abnormally low but this state of affairs is relatively unimportant if the hematocrit *reading and* total red cell mass are approximately normal One may begin by removing 500 cc of blood twice a week and less often as the hematocrit reading approaches normal Later on the removal of 500 cc every one to two months is often sufficient

Irradiation of the long bones and any large mass of blood in the body with roentgen rays inhibits the formation of blood Such treatment can benefit many patients when given in adequate large repeated doses Spray x ray therapy seems to be valuable The effect may last for months or even years before repetition is necessary Serious depression of the white blood cell *forming tissue must be avoided by observations* on the peripheral blood Irradiation of the spleen alone is unsatisfactory and *splenectomy is contraindicated*

Phenylhydrazine hydrochloride because of its ability to destroy red blood corpuscles has been shown to be an efficient therapeutic agent in the treatment of erythremia Its use is less logical than irradiation Acetyl phenylhydrazine is perhaps less toxic than the hydrochloride Patients who have been adequately and carefully treated with these drugs have shown usually a decrease in the concentration of their hemoglobin and red blood cells and have been relieved of most of their symptoms The drugs must be given cautiously in doses determined by the needs *of the patient They are slowly eliminated* partly in the urine which may appear dark brown have a cumulative action and may cause severe anemia Too much is dangerous too little ineffective Following the administration of these substances the products of red blood cell destruction increase and may cause a rise of the bile pigments in the *plasma even jaundice and lead to increased* bone marrow activity When signs of such are present to a considerable extent the drug should be stopped The treatment should also be discontinued when the white blood cell count or the percentage of reticulocytes remains distinctly elevated Treatment guided by frequent blood examinations may begin with 0 1 Gm of actyl phenylhydrazine in capsules per day or every other day by mouth and continued until the red blood cell count has fallen definitely Thereafter at less frequent intervals *0 1 Gm should* be given until a maintenance effect is obtained The action of the

drug is cumulative and patients vary markedly in their response to it By proceeding slowly it is possible to obtain the maximum therapeutic effect with very little danger to the patient As time passes, increasing doses may be necessary In bed ridden patients or those with advanced arteriosclerosis or considerable visceral injury extreme caution should be observed in administering the drug Thrombosis may be precipitated by *phenylhydrazine therapy* The drug should not be given if thrombosis exists or has recently occurred Owing to the prevalence of thrombosis in erythremia effort should be made to keep the patient s circulation active by appropriate exercise and massage

Temporary remissions may be induced by full doses of solution of *potassium arsenite* (Fowler s solution)

Alteration of the type of treatment may be wise Combination of two types of treatment should be considered in resistant cases

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ENTEROGENOUS CYANOSIS

The term "enterogenous cyanosis' was introduced in 1902 by *Stokvis who described* a syndrome of marked cyanosis severe enteritis and clubbing of the fingers in a man of thirty eight without evidence of cardiac or pulmonary lesions or of drug *poisoning* Spectroscopic *examination of the* blood showed the presence of methemoglobin Shortly after, Talma reported three other cases Since then an increasing number of similar cases have been described in which *a marked cyanosis has been observed in* association with methemoglobinemia or sulfhemoglobinemia

Etiology—The cause of this rare condition is unknown but the explanation for the methemoglobinemia or *sulfhemoglobinemia* at times has been attributed to the absorption of toxic products from the intestinal tract in association with the use of various nitrites of coal tar derivatives The reports of cases of methemoglobinemia *and cyanosis* occurring in association with the administration of bismuth subnitrate ammonium nitrate and similar preparations would seem to indicate that these drugs may occasionally be the cause of the *condition* in connection with a chronic gastro intestinal disturbance Instances of sulfhemoglobinemia appear to be associated with the intake of aniline derivatives acetanilid and the like According to *Healy* sulfhemoglobinemia may result from the use of aniline derivatives if there is an excessive amount of hydrogen sulfide in the gastro intestinal tract if insufficient hydrogen sulfide is present *then* methemoglobin will be formed An excellent discussion of the subject has been published by Vogel in his report of a case due to ingestion of sulfur and the absorption of nitrobenzene

Symptoms—The two characteristic clinical features are intense cyanosis and as a rule marked intestinal disturbances both of long duration *Dieckmann* has reported

such a case with methemoglobinemia of twenty seven years' duration Secondary symptoms are weakness dizziness headaches and occasional clubbing of the fingers Dyspnea may be present but usually is not a feature Diarrhea appears to have been noted more frequently than constipation in the cases with methemoglobinemia Patients with sulfhemoglobinemia are usually reported as suffering with marked constipation Moderate anemia may be present

Diagnosis —The diagnosis of the syndrome of enterogenous cyanosis depends largely on the demonstration of methemoglobin or sulfhemoglobin or a combination of both in the circulating blood The existence of cardiac or pulmonary lesions or polycythemia must be excluded If the term is to be correctly used acute cases of poisoning by drugs of the coal tar series potassium chlorate arseniureted hydrogen (sodium dichromate sulfanilamide) or other known causes of methemoglobinemia or sulfhemoglobinemia must be completely excluded Inasmuch as some cases occur without the existence of any known exposure to such compounds it may be that the term enterogenous cyanosis is justifiable As pointed out by Harrop in an excellent review of the subject differentiation between methemoglobinemia and sulfhemoglobinemia can usually be made by the use of a pocket spectroscope applied directly to the lobe of the ear which has been transilluminated by a small flashlight As a rule the cyanosis of methemoglobinemia appears to be more chocolate or brownish in color and affects the skin whereas the patients with sulfhemoglobinemia appear to have a more purplish or lavender color of the lips ears and nail beds with at times a waxy pallor of the skin At times methemoglobinemia and sulfhemoglobinemia are found together

Treatment should aim to improve the associated gastro intestinal disturbance Unlike the more acute cases due to poisoning from aniline dyes and the like no specific poison can be removed Constipation and diarrhea should be treated carefully although in the latter case probably it would be wise to use some preparation other than bismuth subnitrate Cases presenting methemoglobinemia are said to be improved by a diet high in carbohydrate and low in protein A report by Steele and Spink on the use of methylene blue in acute methemoglobin poisoning suggests that such a form of treatment might be applicable in the treatment of enterogenous cyanosis along with measures directed toward improvement of an underlying gastro intestinal condition

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THE LEUKOPENIC STATE

Introduction —Leukopenia may be defined as a lowering of the total white cell count to a value less than that normally observed It is seen in a variety of pathologic conditions and is usually though not invariably accompanied by distinct alterations in the differential count Only rarely does it indicate what is now called agranulocytic angina This fact is frequently overlooked Any one of the constituent types of white cells may be primarily affected but diminution or absence of polymorphonuclear neutrophils is the commonest and most important deviation from the normal

Leukopenia may occur as an incidental though significant finding in certain infectious states such as typhoid typhus Rocky Mountain spotted fever influenza virus pneumonia measles malaria and overwhelming sepsis Thus leukopenia is sometimes a valuable diagnostic aid in sepsis it may be of great prognostic value and may require energetic therapy with such agents as are reported to raise the total white cell count Unquestionably the prognosis of a case with generalized infection due to pyogenic organisms is very grave if the total

count falls below 2000 irrespective of other existing factors unless there be a specific therapeutic agent capable of overcoming the sepsis and thus relieving the leukopenia The leukopenia accompanying sepsis due to pyogenic organisms may show the following types of differential white cell counts (1) a preponderance of mature polymorphonuclear neutrophils, many of which may show the so called toxic granules' (2) a leukemoid picture with many myelocytes and an occasional myeloblast (3) an absence of granulocytes This last type is the most serious and obviously simulates most closely agranulocytic angina In the other diseases mentioned there are no characteristic alterations in the differential count

Leukopenia may also be found in association with certain well defined blood dyscrasias In untreated pernicious anemia a moderate leukopenia is the rule rarely it may become extreme The diagnosis and treatment of such cases is usually clear and the leukopenia itself of little moment Aplastic anemia is characteristically accompanied by a low white cell count and it is important to remember that this sign may occasionally precede all others so that for several weeks the true diagnosis may be in doubt The life of the white cell in the peripheral blood stream is measured in days that of the red cell in weeks Cessation of bone marrow function from whatever cause if all inclusive is therefore first manifested by leukopenia and only later does the more definitive and diagnostic anemia make its appearance

Finally, we are so accustomed to think of leukemia as associated with extremely high white cell counts splenomegaly, and lymphadenopathy that one is prone to forget that this formidable disease may first manifest itself only by vague constitutional symptoms and that the peripheral blood in the initial stages at least may show a moderate or even an extreme leukopenia The diagnostic and therapeutic implications of this fact are obvious It is particularly in children that one is apt to see this atypical onset Other signs of leukemia—myelocytes stem cells (blasts) thrombocytopenia hemorrhagic diathesis increased basal metabolism and changes in the long bones—should be sought for

Leukopenia not infrequently accompanies certain definite pathologic states only indirectly affecting the bone marrow, such as Banti s disease kala azar tuberculosis sarcoid and Hodgkin s disease Banti s disease is one of the commonest causes of marked leukopenia extending over a period of years This fact is of considerable diagnostic value In kala azar the total white cell count occasionally falls to such levels (500-1000) that it becomes in itself of prognostic importance for under these circumstances, as with agranulocytic angina, the patient is particularly susceptible to pathogenic bacteria and death may ensue not by reason of the fundamental disorder but because of these secondary invaders In widespread tuberculosis of the bone marrow there may develop extreme leukopenia and neutropenia, and cases are on record that have closely simulated true agranulocytic angina Curiously enough these hematologic changes may be of a recurrent relapsing type, and I have seen several in which repeated bouts of extreme leukopenia have succeeded each other at irregular intervals and have been followed by the secondary bacterial invasion so commonly seen in agranulocytic angina so that only at autopsy was the true condition discovered Without sternal marrow biopsy it is doubtful if the correct diagnosis can be made under such circumstances In an occasional case of Hodgkin s disease an extreme leukopenia may ensue but in this disease the lymphocytes rather than the polymorphonuclear neutrophils are likely to disappear from the peripheral blood so that one has primarily a lymphopenia

It is well known that a variety of chemical agents some used in therapeusis others in industry may cause leukopenia and neutropenia Chief among these are benzol arsphenamine dinitrophenol gold salts bismuth and sulfanilamide It has long been taught that benzol poisoning was accompanied by an aplastic anemia or pancytopenia and that leukopenia was the first reliable sign of impending trouble From the recent studies of Hunter and his associates however it is apparent that industrial benzol poisoning may bring about the most diverse hematologic pictures and that neither leukopenia nor anemia is an invariable accompaniment When the other chemicals

mentioned affect the bone marrow adversely there usually results an anemia together with thrombocytopenia and leukopenia However dinitrophenol arsphenamine and the sulfonamides *may produce a relatively* pure leukopenia and it behooves all who use these drugs to bear this fact in mind and to watch carefully for its appearance Should leukopenia develop following such medication, it is obvious that the offending drug must be immediately discontinued In the case of poisoning with one of the sulfonamides however the situation is extremely complicated for on the one hand the drugs may cause neutropenia and leukopenia, and on the other they may overcome the sepsis so dangerous to the patient The continuance or withdrawal of the drug and the institution of measures designed to stimulate the bone marrow must therefore be decided in each individual case

HENRY JACKSON JR

AGRANULOCYTIC ANGINA
(*Agranulocytosis*)

Definition.—Agranulocytic angina is an acute fulminating disease characterized by an extreme leukopenia and neutropenia accompanied by ulcerations of the mucous membranes skin or gastro intestinal tract and when untreated leading to death in the great majority of cases

Etiology—This condition was at first not unnaturally presumed to be simply a manifestation of overwhelming sepsis It was not long however before it was noted by Kracke and others including myself that the characteristic hematologic changes preceded the constitutional symptoms and local ulcerations by a matter of several days and it thus became clear that the sepsis was the result rather than the cause of the condition Even so the etiology of the disease remained obscure In 1932 however Kracke noted that most patients had a history of previous medical care or treatment with various drugs containing the modified benzene ring and suggested that agranulocytic angina might well be due to these chemicals This suspicion was amply confirmed by Madison and Squier on clinical grounds and it soon became obvious to all through whose hands any considerable number of these cases had passed that aminopyrine the use of which did not become widespread until 1922, was indeed a very real and perhaps *the commonest cause of this dread* malady In a series of personally collected cases 109 followed the use of some drug Thirty four followed sulfanilamide, eight sulfapyridine thirty nine aminopyrine seven allonal, four causalin In decreasing frequency the following drugs were apparently causative acetanilid amidophen midol cinchophen amytal compound cibalgin bismarsen and neocinchophen It is probable that any of the sulfonamide compounds may cause agranulocytosis and the fact that a disproportionately large number are reported is perhaps the result of the wide use which these drugs have enjoyed Hadler reports a case apparently due to allurate The patient recovered following the use of pentnucleotide and reticulogen This case report raises the serious question of whether agranulocytosis may not be brought on by barbiturates heretofore considered blameless It is important to remember as Rinkoff and Spring point out that fatal agranulocytosis may follow even small doses of any of these drugs and all incriminated should therefore be used with the greatest caution I agree with these authors that such therapeutic agents should seldom be used prophylactically and it may seriously be questioned whether aminopyrine should ever be used except as an analgesic in patients suffering from incurable disease In certain cases the physiologic events of menstruation would appear to be of etiologic importance in this condition but it is well to remember that at such times self medication with coal tar derivatives is common and is often overlooked as an etiologic factor by both patient and physician In a considerable percentage of cases the etiology is still unknown

Women are far more liable to contract the disease than are men Plum found that 80 per cent of his eighty eight patients were women and in my own series of 104 cases almost precisely the same percentage obtained

Agranulocytic angina as we know it at present is a disease of adult life Plum found that it was extremely rare in childhood and

that the incidence rose steadily after the age of twenty five My experience is in agreement with this finding In view of the fact that acute leukemia is a disease chiefly of childhood and that it may at times be most difficult to distinguish from agranulocytic angina these facts relative to age incidence are not without practical diagnostic value

Pathology—The pathologic changes in the bone marrow appear to reflect a maturation arrest at the stem cell (myeloblast) stage In rapidly fatal cases there is an anakmesis of the granulocyte series and a moderate hyperplasia of the precursor stem cells When death occurs after a longer period of illness (eight to fourteen days) there is found hypoplasia of the myeloid tissue, with the coincident appearance of plasma cells and lymphocytes in abnormal numbers Neither the red cells nor the megakaryocytes appear to be materially affected

Symptoms and Signs—It has been repeatedly demonstrated that the first stage of agranulocytic angina is characterized by an extreme leukopenia and neutropenia Thereafter follow the symptoms and signs so familiar to all For obvious reasons this initial asymptomatic leukopenia is rarely recognized The usually observed onset is rapid or sudden with marked prostration high fever headache chills malaise and sore throat When first seen the patient commonly shows a markedly injected and often greatly ulcerated throat There is frequently a brawny edema of the neck and the cervical lymph nodes are usually enlarged and tender, sometimes exquisitely so The temperature is elevated, reaching 100° 103° or even 106° F The spleen is rarely enlarged never greatly so There is no lymphadenopathy not readily accounted for by adjacent infection Jaundice was once considered a *sine qua non* but further clinical experience has shown that this symptom is rare and is to be regarded in all probability as the result of hemolysis or hepatitis due to secondary bacterial invasion

The peripheral blood shows characteristically an extreme leukopenia and neutropenia It is not unusual to find the total white cell count 500 or even less and if the count is above 2500 it is very questionable whether agranulocytic angina is the disease at hand The polymorphonuclear neutrophils are always greatly reduced, and indeed they are frequently absent Eosinophils are virtually never seen at the height of the disease and they may be absent for many months after the acute attack has subsided and the patient has returned to apparent health It is obvious that with a total white cell count of 1000 or less the lymphocytes are also reduced in number This fact is only too often overlooked At the height of the disease it is not unusual to find that 98 or even 100 per cent of the remaining white cells are lymphocytes and in the majority of cases these are of the small normal adult type Occasionally a considerable proportion of the remaining white cells are monocytes It has been said that under such circumstances the prognosis is favorable There is but slight evidence to support this view There is little or no material alteration in the red cell picture though it must be remembered that for various reasons a moderate degree of anemia is not uncommon in middle aged or elderly persons and therefore may well be an incidental finding in true agranulocytic angina However th presence of marked anemia unless explainable upon other grounds strongly militate against the diagnosis of the disease under consideration

Sepsis and ulcerations in and around th throat are so much a part of the usual clinical picture that these findings can hardly be classed as complications In certain cases the ulcerations may become so extensive that the great vessels of the neck are invaded and fatal hemorrhage may result The brawny edema of the neck may cause extreme stenosis of the upper air passages and death by asphyxia Multiple septic infarcts of the lung are occasionally seen Necrosis of the gastro intestinal tract occurs and may be fatal Infection of the skin is common particularly about the face and in rare cases a pemphigus like lesion may result in almost complete dermatolysis in an incredibly short time It should be constantly borne in mind that the patient harbors bacteria throughout his body and that almost any pyogenic complication may therefore result It is further important to remember that during the leukopenic stage foci of infection may give little or no evidence of

their existence but that with the return of the white cell count to relatively normal levels the most diverse manifestations of sepsis may become evident often with surprising rapidity In one case the patient complained throughout the early stages of her disease of pain in the rectum No lesion could be found On the return of the white cell count to 4000 a large ischiorectal abscess developed in the course of forty-eight hours In another case an orbital abscess and cellulitis developed the white cell count rising to 80 000 Autopsy revealed the characteristic findings of agranulocytic angina Such complications developing as the white cell count is rising should be regarded as a sequel to renewed bone marrow activity Pus can not develop during the leukopenic stage Suppuration is the laudable pus of our forebears

Differential Diagnosis—Agranulocytic angina must be distinguished from aplastic anemia, aleukemic leukemia, overwhelming sepsis and diphtheria It is rare that other conditions accompanied by extreme leukopenia (such as Hodgkin's disease) are a source of confusion provided careful attention is paid to signs and symptoms other than the leukopenia Miliary tuberculosis of the bone marrow is an exception to this general rule

Aplastic anemia (pancytopenia) is of course sooner or later accompanied by a marked decrease of the red cell count and a thrombocytopenia These features together with the insidious onset are usually sufficient to differentiate this condition from agranulocytic angina Rarely however aplastic anemia may begin with comparative abruptness and its first hematologic sign may be only leukopenia with relative lymphocytosis Under such circumstances the diagnosis may be difficult until anemia develops It should be remembered that aplastic anemia is common agranulocytic angina extremely rare in childhood

Aleukemic leukemia may be very difficult to differentiate from agranulocytic angina The following points should be borne in mind Acute leukemia is usually a disease chiefly of childhood and early adult life though it may occasionally be seen at any age Agranulocytic angina is practically never seen under the age of fifteen years and is commonest in the older age groups In acute leukemia there are thrombocytopenia progressive anemia and very immature white blood cells (myelocytes myeloblasts lymphoblasts monoblasts) in the peripheral blood A hemorrhagic diathesis is common Marked splenomegaly and generalized lymphadenopathy may occur especially later in the disease In agranulocytic angina the platelets are normal in number anemia of moment does not occur unless occasioned by other causes and the remaining white cells are usually normal appearing lymphocytes though during the stage of recovery immature granulocytes (myelocytes) characteristically appear in considerable percentage The spleen is seldom enlarged never greatly so Lymphadenopathy is found only in association with obvious adjacent sepsis Cases are on record in which what appeared to be true agranulocytic angina has been followed after a period of several months of complete remission by obvious and fatal acute leukemia This fact should make one especially cautious in those cases of apparent agranulocytic angina not preceded by medication with aminopyrine or allied drugs

It may be impossible to distinguish overwhelming sepsis from agranulocytic angina particularly when the polymorphonuclear neutrophils are greatly depressed or absent Commonly however the sepsis is apparent prior to the neutropenia and it is rare to see the extreme neutropenia characteristic of agranulocytic angina

Agranulocytic angina is frequently erroneously diagnosed as diphtheria The mistake is easily avoided if appropriate blood studies are done

Treatment—A number of remedies have been advocated as specific or at least beneficial in this condition In the hands of some physicians good results have followed the parenteral use of liver extract Griffin and Watkins have recommended 300 to 500 Gm of desiccated yellow marrow taken by mouth This method of treatment is definitely limited by the fact that many patients can swallow only with difficulty or not at all Marberg and Wiles have treated patients with extracts of bone marrow It is impossible to draw any concrete conclusions from the small series of cases so treated but the apparent success of this latter method of

therapy should stimulate its further study Other authors notably Forkner, appear to regard any and all forms of therapy as useless Such pessimism does not favor the acquisition of further data regarding the therapeusis of a disease admittedly fatal in some 70 per cent of the cases On the other hand, Goldhamer, Sturgis and Bethel write 'We do not agree with Forkner in labelling as useless all forms of treatment which have been suggested for agranulocytosis It is our opinion that there does exist evidence which suggests strongly that pentnucleotide and blood transfusions are superior to other forms of therapy and should be employed in all cases' Dreverman recommends pentnucleotide and yellow bone marrow both of which agents in his opinion play a role in the maturation of the white cells Strong discussing 'three cases of granulopenia apparently due to infection' says Although the discontinuance of the therapeutic agent (sulfonamide compound) is probably the only measure necessary when the granulocytes reach a low level pentnucleotide appears to accelerate the rate of recovery of the bone marrow and this drug may prove to be a useful therapeutic addendum for us with young patients A combination of attempts to control the infection, discontinuance of drugs which may affect [adversely] the bone marrow, the use of frequent transfusions and the administration of pentnucleotide seems the logical form of treatment Pentnucleotide was first suggested as a form of therapy in 1931 The mortality in a comparatively large series of cases treated with this drug only has been shown to be approximately 35 per cent Ten centimeters of pentnucleotide should be administered intramuscularly four times a day Smaller amounts are ineffective The treatment should be continued until the white cell count has reached a level of at least 5000 and immediately resumed if it should fall again Occasionally unpleasant side affects such as precordial distress nausea or abdominal cramps are seen If the diagnosis of agranulocytic angina seems clear these need not interfere with adequate therapy Only very rarely are the reactions sharp enough to require discontinuance of the drug which at present seems to be the most promising form of specific therapy

The ulcerations in the mouth should be treated with irrigations of saline or glucose The skin should be kept scrupulously clean Fluids must be forced parenterally if necessary

Obviously all drugs suspected of causing the disease must be immediately withdrawn The question of the administration or continuance of the sulfonamide compounds in the presence of extreme leukopenia must be a matter to be decided in each individual case Three points however seem clear First if the agranulocytosis is patently or probably due to the drug the latter should be summarily stopped Second if the agranulocytosis is obviously due to an infection ordinarily amenable to treatment with the sulfonamide compounds (e g pneumococcus pneumonia) these therapeutic agents should immediately be started together with such other measures as the physician in charge believes may help restore the white count to normal levels Third the mere withdrawal of the offending drug does not suffice to restore the white blood cell picture to normal especially if the leukopenia and granulocytopenia has been extreme in spite of a rather general belief that withdrawal is sufficient Such optimism is based largely on reports of cases with moderate leukopenia (e g 3000 white cells of which 20 per cent were polymorphonuclear neutrophils) In any event daily white counts should be done on all cases suspected of having agranulocytosis and energetic measures immediately started if the diagnosis is established If one has faith in any of the therapeutic measures advocated the importance of prompt diagnosis cannot be overemphasized If one maintains a robust pessimism the acquisition of hematologic data is purely of academic interest It is my own belief—and it is shared by others—that all patients under treatment with any drug which has been incriminated should have frequent blood counts and differentials and that if the total granulocyte count should be found very low immediate treatment should be instituted—whether one chooses frequent transfusions yellow bone marrow or pentnucleotide or a combination of one or more of these agents The same holds true of patients with a severe sore throat perhaps the most common initial symptom of agranulo

cytosis It is furthermore imperative that treatment should be intensive—in the case of pentnucleotide no less than 40 cc a day should be given and continued until a favorable response has occurred or until it is apparent that no benefit will accrue

If an analgesic is necessary, codeine will usually suffice to make the patient comfortable morphine may be necessary but should not be used if it can be avoided Complications which would call for surgical intervention in a patient without agranulocytosis should be treated exactly as if the blood picture were normal and just as vigorously

Prognosis—The mortality of the untreated or inadequately treated disease is approximately 70 per cent Death may occur as soon as twenty four hours after the apparent onset or may be delayed as long as three weeks A sustained unremitting high temperature and increasing drowsiness are unfavorable prognostic signs It is obvious that the character and extent of the complicating sepsis play an important role in the prognosis There are few diseases however in which it is more difficult to foretell the outcome I have seen patients recover who on admission were unconscious and had temperatures of 106° F on the other hand patients with but slight elevation of temperature and with white cell count above 1000 have died in spite of all that could be done In general it may be said that once the white cell count has risen to a level of 4000 or more a favorable outcome can be expected while if no hematologic improvement has occurred ten days after the initiation of supposedly remedial measures death is almost certain

Henry Jackson Jr

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THE LEUKEMIAS

Definition—Leukemia is a fatal disease considered by many to be neoplastic in nature which arises primarily in the blood forming organs and is characterized by an extensive and abnormal proliferation of the leukocytes and their precursors Almost invariably at some time during the disease immature white corpuscles appear in the circulating blood frequently in great numbers in most cases there is an associated anemia often of a severe degree

Types of Leukemia and Allied States—For practical purposes it is convenient to discuss the various types under the following divisions

1 Chronic myelogenous leukemia
2 Chronic lymphogenous leukemia
3 Acute leukemia
   (a) Myelogenous
   (b) Lymphogenous
   (c) Monocytic

4 Chronic and subacute *monocytic* leukemia
5 Other varieties and allied pathologic states
 (*a*) Subleukemic leukemia
 (*b*) Lymphosarcoma cell leukemia
 (*c*) Leukemoid reactions
 (*d*) Chloroma
 (*e*) Plasma cell leukemia
 (*f*) Multiple myeloma
 (*g*) Myeloid metaplasia of the spleen of unknown etiology

History —Credit for first establishing the condition as a new clinical syndrome must be given to Hughes Bennett and to Rudolf Virchow In the autumn of 1845 these observers independently and almost simultaneously described in patients after death the greatly enlarged spleen and the increase in white corpuscles in the blood Fuller in 1846 recognized the first case during life The disease was called leukocythemia by Bennett and leukemia by Virchow With the introduction of differential staining methods by Ehrlich in 1891 it became apparent that splenic and myelogenous leukemia were the same The first case of acute leukemia was described by Friedreich in 1857 Lissaurer in 1865 was among the first to employ arsenic in its treatment and observed symptomatic improvement but it was not until 1878 that G E Cutler and E H Bradford made the first careful study of the effect of this drug on the blood Pusey in 1902 introduced roentgen rays in the treatment of leukemia this was followed in 1903 by the observations of Nicholas Senn and in 1904 by those of George Dock on the same subject O Naegeli in 1900 identified the myeloblast and emphasized its importance in relation to the leukemic states *Monocytic leukemia* was first described by H Reschard and Schilling Torgau in 1913

Etiology —There are two principal views concerning the nature of the leukemic process one that the condition is an infection the other that it is a malignant neoplasm The latter is the more commonly accepted theory at present Certainly the condition is an invariably fatal, invasive pathologic process Banti s conclusion in 1904 in regard to the cause of *lymphatic leukemia* epitomizes the most rational present day tentative opinion concerning the etiology of leukemia in general His statement is as follows "A tissue with atypical structure that has a tendency to spread locally from the involved to neighboring organs that forms hematogenous metastases cannot be called hyperplastic it belong instead, in the group of new growths

Those who argue for the infectious *etiology* are influenced to do so because some of the striking features particularly in the acute leukemias, such as chills fever and leukocytosis are also present in diseases of a known infectious nature Infection, especially about the mouth and throat is commonly present, and septicemia may be observed On the other hand it has not been possible to produce leukemia in animals with any organisms which have been isolated from a patient there is no evidence to indicate that the disease is transmissible from man to man, and it is not communicated to the fetus by a mother who has leukemia It is a more logical conclusion that the organisms which have been isolated from patients with leukemia are present in the role of secondary invaders rather than as primary etiologic agents

Additional evidence in favor of the neoplastic theory other than that emphasized in *Banti s statement* given above is as *follows* The disease so far has been produced in mice and guinea pigs only by the actual transference of malignant cells Fowl leukemia is apparently a filtrable form but this is also true of certain types of neoplasms such as sarcomas Maude Slye maintains that spontaneous leukemia in mice follows *the laws of heredity* and is inherited as a simple mendelian recessive characteristic as are other neoplasms

Age and Sex Incidence —Leukemia of various types may be observed in either sex at any age The greatest number of cases of chronic myelogenous leukemia is observed in the decade from thirty five to forty five years whereas the maximum incidence of chronic lymphatic leukemia is between the ages of forty five and fifty four some observers however place its greatest incidence somewhat later namely fifty to sixty nine years It is unusual to observe *chronic leukemia* of either type in patients younger than ten years and it is not likely to occur before the age of twenty five years Acute leukemia occurs *most* frequently in persons younger than twenty five years and has its greatest incidence in children under five years it is very rare in patients older than fifty years but it does occur at any period of life and has been reported in old age

Chronic myelogenous leukemia develops more frequently in males than females in the ratio of 60 40 and chronic *lymphatic*

leukemia is three times as common in the male sex Acute myelogenous leukemia of childhood appears to occur about equally in the two sexes There is no evidence to indicate that leukemia of any type pursues a different course in either sex

Pathology of Various Types of Leukemia—The fundamental pathologic change in any type of leukemia is an extensive proliferation of cells of the myeloid lymphoid or monocytic group which is usually associated with the presence of large numbers of these cells in various tissues of the body and the blood stream

In chronic myeloid leukemia the bone marrow most frequently of the sternum and the long bones is replaced by myeloid cells in which the myelocytes and metamyelocytes predominate although a few myeloblasts may be present A quantitative reduction of the red blood cell forming marrow is the explanation of the commonly associated anemia of the disease The spleen is usually grossly enlarged and there may be a great increase in the myeloid cells of the splenic pulp with often a fibrous thickening of the capsule infarcts are commonly present The liver is usually moderately increased in size and myeloid metaplasia is frequently present in that organ

In chronic lymphogenous leukemia the characteristic pathologic change consists of a replacement of the normal architecture of the lymph glands spleen liver bone marrow and other tissues by lymphoid cells Similar changes may be observed in the tonsils lymphadenoid tissue of the pharynx bronchi esophagus stomach solitary lymph follicles Peyer s patches the bladder and urethra The spleen is usually moderately enlarged due to the lymphocytic infiltration and there may be infarction perisplenitis and thickening of the splenic capsule The bone marrow is almost always involved with a similar lymphoid infiltration which eliminates most of the fat and normal marrow cells

In the acute forms the leukemic infiltrations occur in various tissues throughout the body in a manner similar to that observed in the chronic leukemias In the former however the abnormal collection of infiltrating cells consists almost entirely of myeloblasts lymphoblasts or monoblasts In addition there is commonly a widespread and severe tendency to bleed due to the secondary thrombocytopenic purpura

Symptoms and Signs—The onset is usually insidious and frequently the disease is well advanced when the patient is first examined Definite and pronounced leukemic changes may exist in the blood for several years before the patient complains of symptoms

Frequently the initial complaints are weakness pallor, palpitation and dyspnea which are due to the associated myelophthisic type of anemia In some cases there are no symptoms other than a dull dragging sensation in the left side of the abdomen or a bulging in the left upper quadrant which results from splenic enlargement Fever of an intermittent or remittent type rising as high as 101° or 102° F is commonly observed and this sometimes associated with chills may be an early complaint As an increased basal metabolic rate is commonly encountered in the condition the symptoms due to this such as increased sweating intolerance of warmth loss of weight and tachycardia are frequently present During the acute exacerbations of the chronic form and as a terminal event there may be an abnormal tendency to bleed which manifests itself as epistaxis hemorrhages under the skin from the uterus kidneys bowels or into the retinas or middle ear Cerebral hemorrhage is an occasional complication The hemorrhagic tendency is usually associated with a diminution of platelets in the circulating blood Priapism although always mentioned is an exceedingly rare complication Symptoms associated with an increasingly severe anemia fever and abnormal bleeding are likely to become more pronounced as the disease progresses

The general appearance of the patient varies widely depending largely on the degree of anemia which is present When this is advanced the patient has the aspects of a chronically ill person with pronounced pallor and emaciation In the earlier stages when the red blood cell count and hemoglobin are within normal limits the appearance may be that of a robust person in good health although even then the white blood cell count may be several hundred

thousand per cubic millimeter and the spleen greatly enlarged

Splenic enlargement, sometimes to a degree which causes this organ to occupy a greater portion of the abdominal cavity is characteristic of the disease The lower edge commonly reaches below the umbilicus The absence of a palpable spleen is strong evidence against the diagnosis of chronic myelogenous leukemia The organ is firm and is not tender unless perisplenitis develops The liver is usually palpable and may attain an enormous size

Characteristically the lymph nodes are not enlarged as they are in the lymphatic type and this assists in differentiating the two types of the disease Occasionally there may be a moderate increase in size of some of the lymph glands due to an infiltration with myeloid cells similar to that which occurs in other tissues of the body

Skin lesions other than the purpuric manifestations are not a commonly encountered complication In some instances there is an infiltration of the skin with myelocytes and myeloblasts which causes the formation of bluish gray, elevated nodules varying in size from a pin head to a walnut They most frequently appear on the trunk although they have been observed elsewhere on the body Ordinarily they are not associated with itching or pain

As leukemic infiltrations may be present in almost any tissue of the body the possible complications are many In addition to those already mentioned the following may occur the retinae may show hemorrhages and leukemic infiltrations there may be destructive lesions of bone with pathologic fracture deafness can occur due either to hemorrhage or leukemic infiltrations in the inner or middle ears various lesions of the nervous system may be observed which are due either to hemorrhages thromboses or tumor like infiltrations hematuria associated with infiltration of the kidneys may be encountered, myeloid changes may occur in the gastro intestinal tract resulting in hemorrhage but this is more frequently observed in lymphatic leukemia

Blood Examination—The typical blood picture is an increase in the total number of leukocytes to 100 000 or more per cu mm of which from 20 to 60 per cent are myelocytes chiefly in the later stages of development and from 30 to 70 per cent are polymorphonuclear neutrophils with segmented nuclei An occasional myeloblast may be seen As the disease progresses the proportion of myelocytes and myeloblasts increases and in the advanced or terminal stages 70 per cent or more of the cells may be of the latter type The total white blood cell count usually ranges between 100 000 and 500 000 per cu mm although as many as 1,000 000 or more leukocytes per cu mm have been observed It is not rare for the leukocyte count to become normal or for a leukopenia to develop either spontaneously or following treatment This is discussed in the section on Subleukemic Leukemia An almost constant finding is an increase of from 2 to 10 per cent of basophils and occasionally these cells may comprise 50 per cent or more of all the leukocytes (basophilic leukemia) Likewise the numbers of eosinophils and eosinophilic myelocytes are frequently increased to 5 or 6 per cent of the total leukocytes and in some instances these types of cells are the predominating ones in the circulating blood (eosinophilic leukemia) Monocytes are usually present but rarely exceed 3 per cent of the total number of leukocytes There is characteristically a decrease in the percentage of lymphocytes but their absolute number may be normal or actually increased Care should be used in differentiating between lymphocytes and myeloblasts

Most frequently there is a slight increase in the blood platelets above normal but this may be excessive or in some instances the numbers may be reduced sometimes to a marked degree The latter change usually prevails in the more acute and terminal stages of the disease and is often associated with a hemorrhagic tendency Occasionally an experienced observer may detect megakaryocytes in the blood

An anemia is an almost constant finding at some stage during the course of every case of leukemia It is usually normocytic in nature as almost always the mean corpuscular volume mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration are within normal limits At the onset or following spontaneous or therapeutically induced remissions it is often mild

or may be absent The general condition of the patient usually parallels the level of the red blood cell count and hemoglobin percentage It is generally accepted that the anemia is of the myelophthisic type which results from the encroachment of the hyperplastic myeloid tissue in the bone marrow on the red blood cell forming elements causing a diminished rate of erythrocyte production In the bone marrow there often remain areas of erythrocytic activity which as a compensatory mechanism may account for the presence of reticulocytes and nucleated red blood cells in the circulating blood

Prognosis —There are no authentic cases on record in which a patient with myelogenous leukemia has recovered It is generally agreed among authorities that the average duration of life is between two and one half to three and one-half years after symptoms appear and that irradiation will prolong life for an average of only about six months at the most Undoubtedly the characteristic blood changes precede the onset of symptoms in some cases by a period of several years Although the average duration of life is short over 10 per cent of the cases survive for a period of five to ten years after the onset of symptoms and instances are known of patients who have survived as long as sixteen years

The great benefit derived from treatment is not the prolongation of life but the improvement of symptoms and the temporary restoration of a patient to apparent health for considerable periods of time A study of the natural course of the disease indicates that spontaneous remissions occur in less than 10 per cent of the patients The proper use of irradiation however will improve the patients markedly in fully 50 per cent of the cases and permit them to lead efficient lives for 50 to 75 per cent of the period between the beginning of treatment and death The results attained are much better when treatment is applied as soon as the earliest indications for it appear the effect when used later in the course of the disease however is worth while Judging by the improvement in the anemia the response in chronic myelogenous leukemia is better than it is in the chronic lymphatic type

Regardless of the method with which irradiation is used there inevitably comes a time when it produces little improvement in the blood or the clinical condition of the patient Emaciation develops fever is often a prominent feature the anemia becomes progressively worse a hemorrhagic tendency may develop and death usually ensues in from four to six months after the onset of the period of decline

CYRUS C STURGIS

CHRONIC LYMPHOGENOUS LEUKEMIA

The onset is insidious usually with one or two types of complaints namely the patient observes either a painless nontender lymph node in the neck axillae or groin or the symptoms of an anemia develop such as pallor weakness ease of fatigue dyspnea and palpitation Less frequently the initial symptom may be the occurrence of an abnormal tendency to bleed as indicated by hemorrhages from the mucous membranes or excessive bleeding following trauma Occasionally an early symptom may be associated with a leukemic infiltration of the skin which causes itching and redness In some instances the disease has been discovered as an incidental finding of a lymphocytosis when a routine blood examination has been done

The commonly encountered findings on physical examination are associated with the anemia the enlarged lymph glands and splenomegaly Usually the patient appears pale and gives a history of recent increasing pallor and loss of weight Evidences of abnormal bleeding are not ordinarily observed except during acute exacerbations of the disease and as a terminal event The lymph nodes are most frequently enlarged in the cervical axillary and inguinal regions They vary in size from a pea to a hen s egg and are nontender smooth moderately firm and are not adherent to each other Usually they increase slowly in size unless reduced with radiation therapy it is not common to have them diminish in extent spontaneously although it has been claimed that this may occur following an intercurrent infection Roentgenograms may disclose an increase in the extent of the mediastinal lymph glands

but rarely is it possible to palpate enlarged abdominal glands Occasionally cases have been reported without enlargement of the lymph glands but such a situation is exceedingly rare The firm nontender edge of the spleen is most often palpable 7 to 8 cm below the left costal margin but never is a huge size attained The liver is usually moderately enlarged

Blood Examination —It is ordinarily not difficult to conclude, from the blood examination alone that a patient has chronic lymphatic leukemia This is because usually the total leukocyte count is increased to from 30 000 to 100 000 per cu mm and from 60 to 90 per cent of the cells resemble the normal small lymphocytes In the early stages the red blood cell count and hemoglobin percentages are normal but eventually a normocytic anemia will develop and as the disease progresses it almost always reaches a severe degree The number of blood platelets is characteristically decreased to a moderate extent, although they may at times show a slight increase The difficulty in recognizing the disease arises when the total white blood cell count is normal or below normal and the diagnosis from a study of the blood depends primarily on the recognition of the immature forms of lymphocytes This is also puzzling in the acute phases when a very large percentage of the cells are immature as even experienced observers in hematology cannot always agree upon the criteria for differentiating immature lymphocytes from myeloblasts Although the various stages of the myeloid cells are easily recognized, this is not true of the lymphocyte series In general the immature lymphocyte differs from the fully developed form in that the former is more commonly a large cell with comparatively large nucleus some believe that the nuclear pattern serves to differentiate it from the myeloblast It is generally accepted that the degree of basophilia of the cytoplasm parallels the age of the lymphocyte series and that young lymphocytes and lymphoblasts have a more basophilic cytoplasm

There is a marked diminution or almost complete absence of monocytes polymorphonuclear neutrophils eosinophils and basophils

The Basal Metabolic Rate in Chronic Leukemia —The basal metabolic rate in untreated patients with either chronic myelogenous or lymphogenous leukemia may be elevated above normal limits although the increase is moderate usually varying between +20 and +30 occasionally the elevation may be more extreme reaching levels as high as +70 or +80 It should be recognized that some of the important manifestations of the disease depend on an increased basal metabolic rate These are dyspnea tachycardia sensation of increased body warmth excessive sweating intolerance to heat and loss of weight These symptoms however, are never as conspicuous as they are in patients with toxic goiter who have a similarly elevated basal metabolic rate Often in leukemia the level of the basal metabolic rate is a more accurate index of the clinical condition of the patient than either the white blood cell count or the percentage of immature myeloid cells in the circulating blood High estimations which persist despite irradiation suggest a poor prognosis

The cause of the increased basal metabolic rate is not definitely known but it is considered to be due in large part to the increased consumption of oxygen by the leukemic cells throughout the body An accelerated rate of destruction of these cells may also be a factor of importance in this connection

Prognosis —Chronic lymphatic leukemia resembles other types of the disease in that it is an invariably fatal condition The average duration of life is about three and one half years If the period of survival is considered in a large group of patients either treated or untreated it will be found that about two thirds of them die between one and four years from the onset of symptoms one fifth in four to six years and one tenth in six to eight years a few succumb in less than a year Irradiation even when efficiently employed early in the course of the illness does not materially prolong the life of the patient Although the beneficial results in this form of leukemia are not as striking as they are in the chronic myelogenous form they are distinctly worth while About one half of the patients show moderate and 10 per cent striking improvement following irradiation The failure of response of a patient to x ray is a reliable but unfa

vorable aid in prognosis for it usually indicates that a fatal outcome is to be anticipated in a matter of months In such patients often over 50 per cent of the circulating white blood cells are immature lymphocytes and when this occurs it is strongly suggestive evidence that the patient will not survive for a longer period than six months

Treatment of Chronic Leukemia.—It is generally accepted that leukemia is an invariably fatal disease but that the roentgen rays may produce worth while benefit when employed as a symptomatic form of treatment Arsenic especially in chronic myelogenous leukemia is of use but less effective Benzol and splenectomy are no longer considered to be of value radium although it produces beneficial effects is ordinarily less convenient to apply and possesses no advantages over the x ray blood transfusions are of limited value but are desirable in certain phases of the disease

Treatment with the Roentgen Rays—It should be emphasized that this therapeutic agent should be applied *only* when important symptoms warrant its use The most commonly encountered indications are as follows pressure symptoms resulting from enlarged glands or the spleen loss of weight which is frequently associated with fever and a persistently elevated basal metabolic rate symptoms referable to an increasingly severe anemia of which the most significant are weakness and ease of fatigue involvement of important regions of the body with leukemic infiltrations and the occurrence of purpura and spontaneous bleeding from the mucous membranes

The *contraindications* which should be carefully evaluated before irradiation is employed are now well recognized It is known that in acute leukemia of any type or in an acute exacerbation of chronic leukemia x ray therapy is valueless and commonly does more harm than good While the presence of as many as 50 per cent of myeloblasts or lymphoblasts is not in itself enough to deter treatment with x ray it should be applied with caution when these circumstances prevail and probably little benefit will result Following the appearance of a hemorrhagic tendency or a leukopenia which arises spontaneously the x ray should be used with extreme care if at all and then it is unlikely to improve the condition of the patient If either of these situations develops during the course of treatment it is a definite indication to stop immediately all roentgen ray therapy The presence of a severe anemia does not prohibit the use of x ray therapy but it is advisable in such patients to precede the x ray exposures with several blood transfusions and to discontinue further roentgen ray therapy if the anemia becomes more severe

The usual form of therapy has been to employ the following physical factors 200 kilovolts (peak) filtration of 0.5 mm copper plus 1 0 mm aluminum (H V L 0 9 mm copper) distance of 50 cm, and a dose of 100 to 200 r measured in air to parts ranging from 10 × 10 to 15 × 15 cm per treatment Such an exposure is given each day usually for eight to twelve days Caution should be used in the application of roentgen therapy as not all patients will tolerate the maximum treatment outlined above and the reaction is often unpredictable It is advisable that the initial treatments should consist of smaller doses applied to more limited fields

A valuable guide to roentgen ray dosage is the level of the leukocyte count Rarely is it advisable in a patient who has pronounced leukocytosis at the beginning of treatment to continue the therapy after the count falls to 25 000 or 30 000 per cu mm The maximum effect of therapy often does not become apparent until several days after exposure Patients who have an initial leukocyte count of less than 20 000 per cu mm should be given a decreased dosage the interval between the treatments should be lengthened and the white blood cell count made daily as a guide to treatment

Treatment with Arsenic—Recently Forkner has revived an interest in the use of arsenic and believes that it has a distinct value in chronic myelogenous leukemia It may also be of benefit in the lymphatic form but does not cause improvement in the acute types of the disease even though it may produce a reduction in the total leukocyte count Apparently the drug fails to act in patients who have become refractory to irradiation It is worthy of a trial however when high voltage x ray is not available

and it has the advantage of being less expensive Forkner* recommends that arsenic in the form of Fowler's solution be given as follows "Begin with doses of about 5 minims (0 3 cc) three times daily for two days, preferably in orange juice immediately after or with meals On the third and fourth days give 6 minims three times daily and continue increasing in this manner to about 10 minims three times daily, thereafter increasing by 1 minim per day until toxic symptoms are pronounced or until the leukocyte count approaches normal Thereafter omit medication for from two to five days and then decrease the dose from the maximum by 1 minim per day down to a maintenance dose of from 5 to 8 minims three times daily Continue this dosage indefinitely' All toxic manifestations of the drug such as anorexia nausea vomiting and diarrhea disappear in forty eight hours after it is discontinued and it may then be given again in slightly smaller doses

Treatment with Radio active Phosphorus—This is the most recent form of treatment employed in patients with various types of leukemia Although experience with it is limited it is possible to make the following tentative statements (1) it is effective therapeutically when given orally as sodium phosphate dissolved in water and does not produce important untoward symptoms (2) it is effective in both myelogenous and lymphogenous leukemia but some claim that better results are attained in the former, (3) the indications and contraindications for the use of radio active phosphorus in leukemia are the same as those commonly accepted for roentgen ray therapy (4) although the optimum dosage has not been finally determined an average course of treatment for a patient weighing 70 kg would total approximately 25 to 50 millicuries divided into six or seven equal doses given at weekly intervals As in roentgen ray therapy however it is essential that the amount of treatment be guided by frequent blood examinations with particular reference to the leukocyte count and the total number of immature cells

The Use of Blood Transfusions—The transfusion of blood should be considered as a palliative measure in all patients with a severe anemia or those in whom purpuric manifestations are present Temporary improvement may follow in those who have not responded favorably to roentgen ray or arsenic therapy Furthermore, in the presence of a severe anemia several transfusions of from 400 to 600 cc of blood should be given before these forms of therapy are employed

CYRUS C STURGIS

* Forkner Claude E. Leukemia and Allied Disorders By permission of The Macmillan Company Publishers

ACUTE LEUKEMIA

At least three varieties of the acute type of the disease undoubtedly do occur Frequently however the mode of onset, the signs and symptoms the course of the disease the changes in the circulating blood and the pathologic findings at necropsy, are so similar that recognition of the particular type in any given case may be impossible This is because almost all of the circulating leukocytes may be of the very immature type and as a result difficulty arises in classifying them as either myeloblasts lymphoblasts or monoblasts

Symptoms and Signs—The onset of acute leukemia is usually rather abrupt with the development of symptoms which are often considered to be due to a cold or upper respiratory infection an ulcerative stomatitis or acute tonsillitis There is ordinarily no suspicion as to the serious basis for the complaints until attention is directed toward the rather sudden appearance of pallor indicative of a rapidly developing anemia or an unusual degree of prostration which is out of proportion to the minor nature of the initial symptoms Fever which may be associated with outspoken *chills o* chilly sensations is almost invariably present in the advanced stages but an increase in body temperature may also occur early

A spontaneous hemorrhagic *tendency* is commonly present and is usually a manifestation of a secondary *thrombocytopenic* purpura with the characteristic decrease in *blood platelets* It may be one of the early indications of the sinister nature of the patient's illness Bleeding occurs into the skin and from the mucous membranes of the mouth the gums or the nose into the

fundi of the eyes and the brain from the gastro intestinal tract and the uterus The first evidence of the disease may be profuse hemorrhage following the extraction of a tooth removal of the tonsils or from minor injuries Although a slight tendency to bleed may be noted early in the illness the more extensive hemorrhagic manifestations occur late as a rule and their appearance is usually an ominous sign

Blood Examination —The characteristic change in the blood is the presence of a large number of mononuclear, nongranular cells which are usually either myeloblasts or lymphoblasts rarely are they monoblasts Frequently almost all of the cells are of a uniform immature type and confusion arises as to their exact identity Very few, if any intermediate cells representing stages between the mature and the primitive forms may be present a fact which makes difficult the recognition of the predominant primitive cell type It then becomes necessary to depend upon the cytologic characteristics of the myelocyte lymphocyte and monocyte in order to classify the type of acute leukemia from which the patient is suffering This is not possible in all instances even by experienced hematologists in such cases therefore it is necessary to be content with the diagnosis of acute leukemia of undetermined type The total number of leukocytes in the various types of the disease is most frequently between 15 000 and 30 000 per cu mm rarely does the count exceed 100 000 per cu mm At the onset it is commonly below 8000 per cu mm and it may be 2000 to 3000 per cu mm or less

The characteristic alteration in the circulating blood in acute myelogenous leukemia is the presence of immature cells of the myeloid series As previously mentioned almost all of the white corpuscles may be of the myeloblast type which closely resembles both the lymphoblast and the monoblast There is a parallelism between the number of myeloblasts and the acuteness of the disease In the subacute myelogenous variety the intermediate cell stages promyelocytes and myelocytes are present and classification can be made without difficulty In acute lymphatic leukemia some of the cells may be in the intermediate stage between the lymphoblast and the mature lymphocyte As the large cells represent the more immature lymphocyte it is this type that predominates in acute lymphatic leukemia whereas the small lymphocyte is the commonly encountered cell in chronic lymphatic leukemia

A severe anemia almost always develops in the acute leukemias in which the red blood cells may fall to 1 000 000 per cu mm or less in some cases there may be nucleated red blood cells and an increase in reticulocytes The blood platelets are almost always reduced in number

Prognosis —The disease frequently has a fulminating course and terminates fatally within a relatively brief interval More than three fourths of the patients succumb within eight weeks after the appearance of the initial symptoms and about one fifth die after an illness of two or three weeks There is no authentic record that a patient with true acute leukemia has ever recovered Occasionally the disorder will change spontaneously from the acute to the subacute or chronic phase but this is rare and even then the duration of life is ordinarily not greater than six months

Treatment —The treatment of the acute leukemias is ineffective Irradiation usually produces more harm than benefit and is contraindicated except in exceedingly small doses Repeated blood transfusions may cause some transient improvement by increasing the red blood cell count and hemoglobin percentage and in rare instances the acute phase may change to the chronic type which is more amenable to irradiation transfusions may also control temporarily the tendency to bleed through the introduction of platelets into the circulating blood

CYRUS C STURGIS

MONOCYTIC LEUKEMIA

Within recent years it has been recognized that a leukemia may occur which differs from other types in that there is a significant increase in the cells of the monocyte series in the circulating blood The characteristic pathologic change is an infiltration of the organs of the body especially the spleen and the liver with monocytic cells resembling those of the blood

There is no agreement concerning the origin of the monocytes but there is strong evidence that they are an independent strain of cells Undoubtedly a leukemia does occur which has acute, subacute chronic and aleukemic phases and in which the chief characteristic in common is the presence of an increased number of monocytes in the blood some of which may be immature in type Distinctive clinical features appear to be the frequent occurrence of oral lesions such as gingivitis and angina and a tendency for the patients to develop purpura and bleeding from the mucous membranes Enlargement of the liver and spleen may be observed but it is uncommon and when present is usually of slight extent The course is usually rapid and a fatal termination commonly occurs within a period of months

Downey recognized two varieties of monocytic leukemia—the Schilling type in which the monocytes are derived from the reticulo endothelial system and the Naegeli type in which the monocytes are supposed to develop from the myeloblasts, thereby making this form a variant of myelogenous leukemia Although the mature monocytes are identical in both varieties their origin is entirely different There are no significant differences in the clinical picture between the types of the disease or other forms of leukemia The recognition of the two types of monocytic leukemia is based solely on hematologic grounds In the Naegeli variety the peripheral blood contains a predominance of monocytes in various stages of development in association with a number of myeloblasts and young myelocytes In the Schilling type, monocytes usually fairly mature predominate and larger histiocytes may be found Myeloblasts are absent from the peripheral blood but an occasional myelocyte may be present

Blood Examination—The white blood cell count is usually between 25 000 and 100 000 per cu mm although extreme variations may be from 2000 or 3000 to several hundred thousand The monocytes usually make up 50 per cent of all white blood cells occasionally 90 per cent In patients with the chronic form of the disease almost all of the monocytes resemble the normal adult form The monoblast is described as a cell having a nucleus with a density similar to the lymphoblast and myeloblast As the cell develops the bluish shade of the cytoplasm in films becomes less deeply stained and finally resembles the light blue mottled cytoplasm of the mature cell

CYRUS C STURGIS

UNCOMMON VARIETIES OF LEUKEMIA AND ALLIED PATHOLOGIC STATES

Subleukemic (Aleukemic) Leukemia—Confusion in regard to this condition is in part due to the many names applied to it In the past it has been designated pseudo leukemia aleukemic myelosis aleukemic lymphadenosis aleukemic monocytic leukemia pseudoleukanemia aleukemic erythroblastosis and many others These should all be superseded by the term subleukemic leukemia'

In order to clarify the situation it should be emphasized that there may be a stage of either chronic subacute or acute myelogenous lymphatic or monocytic leukemia in which the white blood cell count is either normal or actually below normal Almost always there are a variable number of immature white blood cells in the circulating blood and often by sternal puncture it is possible to demonstrate a characteristic leukemic change in the bone marrow In some cases the leukocyte count remains apparently normal or below throughout the illness more commonly there have been transient or prolonged increases to 30 000 or 50 000 per cu mm or higher This may occur at any time during the course of the disease but it is more likely to be observed as a terminal event These spontaneous increases in the number of leukocytes are the most convincing evidence that subleukemic leukemia is a variety of the more commonly encountered type and varies from it chiefly in the changes observed in the circulating blood Occasionally leukemic changes have been demonstrated at necropsy in patients in whom it has been claimed that immature white blood cells have not been present in the circulating blood and that the total leukocyte count has never been elevated

This situation may be exceedingly rare and in such reported cases one suspects that if the circulating blood had been examined more frequently during life, immature white blood cells would have been noted

The clinical picture in such patients depends to a certain extent upon the variety of subleukemic leukemia which is present There are variable degrees of splenomegaly and lymphadenopathy but in some cases these findings may be absent The most common clinical features are as follows (1) A progressive normocytic normochromic anemia often reaching a severe grade associated with this are the customary complaints of weakness ease of fatigue dyspnea and palpitation on exertion Aplastic anemia is the condition most commonly confused with subleukemic leukemia but it is necessary also to distinguish from it pernicious anemia Hodgkin s disease myelophthisic anemia resulting from metastasis in bones and achrestic anemia (2) The anemia of this disease is refractory to all forms of treatment Aside from the temporary improvement following blood transfusions none is observed except that associated with rarely occurring spontaneous remissions (3) The total white blood cell count is frequently below 4000 per cu mm and may be as low as 1000 or 2000 per cu mm In almost every instance there are immature white blood cells present in the circulating blood but as they are scarce and the total white blood cell count is usually diminished they may be easily overlooked even by the expert hematologist It is not uncommon for the less experienced to regard the myeloblasts which may be present as lymphocytes It should be emphasized that careful examination in almost all instances will show that the differential formula is abnormal (4) Sternal puncture may assist in the diagnosis as it may show the predominating cells of the marrow to be myeloblasts lymphoblasts or monoblasts Unfortunately from a diagnostic standpoint the sternal marrow is not infiltrated with abnormal cells in all cases of subleukemic leukemia The examination is of greatest value in demonstrating positive evidence of the disease a normal sternal marrow does not eliminate it as a diagnostic possibility (5) It is important to emphasize that there is commonly a decrease in the circulating blood platelets which may or may not be associated with purpuric manifestations such as bleeding from the mucous membranes retinal hemorrhages and petechiae

One should always consider the diagnosis of subleukemic leukemia in the presence of any one or a combination of the following (1) a leukopenia with or without an associated normocytic or macrocytic anemia (2) an unexplained lymphadenopathy or splenomegaly (3) fever without obvious explanation (4) tumefaction of the gums (5) a hemorrhagic tendency (6) certain characteristic skin lesions (7) vague pain in the bones and about the joints and (6) bone tenderness especially if it involves the sternum

Lymphosarcoma Cell Leukemia.—Lymphosarcoma cell leukemia is a definite clinical entity characterized by the presence of lymphosarcoma cells in the blood stream These vary in size from 12 to 14 microns in diameter and have a sparse but deeply basophilic cytoplasm The most striking identifying feature of the cell is the nucleolus which is usually single eccentrically placed and light blue in color When stained with cresyl blue and Wright s stain it is surrounded by an intensely staining conspicuous blue black rim

Such a type of leukemia arises when lymph tissue undergoes sarcomatous change which at first is a localized new growth Eventually the neoplastic cells escape from the confines of the surrounding tissue and appear in the blood stream The earliest evidence of the disease is usually enlargement of the lymph glands or spleen or symptoms referable to the anemia Throughout the course of the disease anemia fever hemorrhage and infection are the most conspicuous features The condition occurs most commonly in males it may appear at any age Frequently the condition manifests itself at a time when the blood does not exhibit abnormal changes It may be months or even several years before the lymphosarcoma cells invade the blood stream When this occurs the course is usually rapid although beneficial effects may follow the cautious employment of roentgen therapy About one half of the patients die within one year after onset of symptoms or

discovery of the tumor Patients with this condition are usually regarded as suffering from lymphatic leukemia, the careful exclusion of such cases will extend the average duration of life of patients with lymphatic leukemia to four or five years which is longer than usually stated

Leukemoid Reactions —It is now appreciated that there are a considerable number of conditions, in addition to true leukemia in which immature white blood cells may appear in the circulating blood in association with a normal, increased or decreased leukocyte count Such a blood picture is called a *leukemoid reaction* This highly important differentiation can usually be accomplished by continued clinical observation repeated blood examinations and a study of the sternal marrow

As the hematopoietic tissues in infancy and childhood are more likely to react abnormally to various stimuli especially infections caution should be used before concluding that the hematologic changes in the blood of a young person are of a leukemic nature Confusion is more likely to arise with the alterations observed in the acute leukemias In this condition three important and almost constantly occurring changes are helpful in differentiating it from a leukemoid reaction (1) 60 to 70 per cent or more of the circulating white blood corpuscles are of the uniformly large immature blast" type (2) a normocytic or slightly macrocytic anemia often of severe grade usually develops during the course of the disease (3) the blood platelets are almost always reduced in number

Lymphatic leukemoid reactions are observed in a number of diseases including pertussis typhoid fever and infectious *mononucleosis* The latter condition which is characterized by complaints referable to the upper respiratory passages fever lymphadenopathy a palpable spleen in 50 per cent of the cases and atypical lymphocytes in the circulating blood, should receive most careful consideration in all young persons in whom the diagnosis of leukemia is a possibility Of considerable assistance in the differential diagnosis is the heterophile antibody reaction which is usually positive in infectious mononucleosis and negative in leukemia

Leukemoid reactions of the myeloid type are observed occasionally in almost any type of pyogenic infection A pyonephrosis in which the infected kidney may be mistaken for the spleen when it is on the left side if associated with a leukemic blood picture may present a most puzzling diagnostic problem Immature leukocytes may also be present in nonpyogenic infections such as subacute bacterial endocarditis and tuberculosis Similar changes may be observed in various hemolytic anemias of which congenital hemolytic icterus sickle cell anemia and Lederer s anemia are examples Other blood dyscrasias including pernicious anemia especially at the beginning of a remission polycythemia vera erythroblastic anemia and anemia following hemorrhage may be associated with such blood changes A special group in which a leukemoid blood picture may be present consists of pathologic processes which involve the bones and bone marrow Examples of such conditions are metastases from malignant processes multiple myeloma and osteosclerosis Lastly immature white blood cells may be noted in the blood stream of patients in diabetic coma in poisoning with mustard gas mercury, and phenylhydrazine and occasionally in cases in which the cause cannot be ascertained

Chloroma —*This disease is a rare variety* of leukemia characterized by an invasive tumor like growth of greenish color in various organs and tissues of the body and by changes in the blood simulating closely those seen in acute myelogenous *leukemia Often* many of the white blood cells are of the mononuclear nongranular type which so commonly occur in acute leukemia and the same difficulty arises in classifying these changes into the lymphatic or myelogenous variety Most present-day observers believe that they are myeloid cells

The greenish tumors may be observed in any tissue in which leukemic infiltrations are known to occur The bones of the skull are involved with relative frequency a tumor of the orbital fossa causing exophthalmos was present in 11 of 18 cases collected by Dock and Warthin Tumors may occur in the lymph nodes spleen kidneys and many other organs and tissues The bone marrow may have a uniformly greenish color or circumscribed areas of pigmentation

The condition is observed more frequently in males than in females and has its greatest incidence in childhood adolescence or young adult life It is similar to acute leukemia in that it has a brief course which usually terminates fatally in a few weeks or months All types of therapy which have been employed are ineffective

Plasma Cell Leukemia —A statement concerning this exceedingly rare condition is included for the sake of completeness Plasmacytomas or tumors in which the type cells are plasma cells are regarded as neoplasms which may be localized or metastasizing new growths They are observed in the bones the upper respiratory passages the conjunctiva the cornea the pleura and elsewhere In contrast to this type of plasmacytoma there is a diffuse form which is characterized by an extensive infiltration of plasma cells into the bone marrow the lymphoid tissue and the liver and spleen Such an alteration simulates closely the characteristic changes in tissue which are seen in the well known varieties of leukemia except that the infiltrating cells are plasma cells

In some instances these pathologic changes are not associated with the presence of plasma cells in the blood in others small numbers are observed in some which may be regarded as true plasma cell leukemias the total white blood cell count may be greater than 50 000 per cu mm of which 25 to 50 per cent are plasma cells

Multiple Myeloma.—*Definition.*—Multiple myeloma is a neoplastic like growth which involves the skeletal trunk with destructive lesions causing pain pathologic fractures and anemia It is usually associated with the presence of Bence-Jones protein in the urine and blood

Although it has not received general acceptance the most satisfactory tentative view is to consider multiple myeloma as a neoplastic process in which the myeloid cells are derived from the hematopoietic system If this is true the condition bears a close relationship to leukemia The cells making up the tumors have been most commonly regarded as plasma cells although their identification is by no means definite Possibly myeloma cells are a distinctive type varying from all other forms

Symptoms and Signs—The condition is observed twice as commonly in males as in females Almost all cases occur after the age of forty years Pain of a vague intermittent shifting type often referable to the spine is commonly the earliest evidence of the disease As the condition progresses this frequently is a severe and dominant symptom Tumors and pathologic fractures usually in bones containing red marrow are common Changes in the spine causing compression of the spinal cord with its resultant neurological manifestations is not a rare complication

Blood—A moderately severe normocytic or slight macrocytic normochromic anemia is almost always present The leukocyte count is ordinarily normal slightly elevated or diminished and the differential formula is usually not disturbed or may reveal only an occasional abnormal white blood cell. Rarely have many plasma cells been observed in the blood stream but these when present have caused the condition to be regarded as a plasma cell leukemia

A finding of great diagnostic importance is the presence of Bence Jones protein in the urine which appears in about two thirds of the cases It is said to occur occasionally in the urine of patients with leukemia and polycythemia This protein precipitates at temperatures of 50° to 60° C, further heating causes it to go into solution at about boiling and on cooling it reappears Its presence appears to be limited to pathologic conditions attacking the bone or bone marrow There may be a pronounced hyperproteinemia as indicated by plasma protein determinations which are often found to be 10 Gm per 100 cc of plasma or above figures twice as high as this have been reported This is due entirely to an increase in the globulin fraction Autohemagglutination or spontaneous clumping of the erythrocytes occurs in some cases This accounts for the tendency to striking rouleau formation and an accelerated sedimentation rate Serum calcium is frequently elevated to levels of 12 to 16 mg per cent but the serum inorganic phosphates are usually normal

In addition to those mentioned above there are two diagnostic procedures which are of great importance (1) sternal puncture which usually reveals the presence of

typical myeloma cells, and (2) roentgen ray examination which demonstrates the characteristic punched out areas, without evidence of bone regeneration in the ribs spine, clavicles skull and the shoulder and pelvic girdles

Prognosis and Treatment —The disease is uniformly fatal after an average duration of life of between two and three years Occasionally the course is prolonged with remissions and exacerbations Roentgen ray exposures should be employed in all cases as it frequently gives worth while symptomatic relief and may prolong life in some instances This with blood transfusions is the only known therapeutic agent of recognized value Otherwise the treatment is symptomatic

Myeloid Metaplasia of the Spleen of Unknown Etiology —This condition has been described by Henry Jackson Jr and his collaborators as one which closely simulates chronic myeloid leukemia It is characterized by weakness abdominal distress a hemorrhagic tendency and a slowly progressive enlargement of the spleen due to the myeloid metaplasia The hematologic picture is almost identical with that of myelogenous leukemia but it may resemble chronic hemolytic jaundice Usually there is a moderate elevation or slight depression of the white blood cell count, immature white and red blood cells are present in the blood stream The changes in the spleen and bone marrow differentiate the condition from myelogenous leukemia In the former, the malpighian corpuscles are preserved infarction is absent, and the marrow may appear normal aplastic hyperplastic or fibrotic but never resembles the alterations observed in leukemia The diagnosis of myeloid metaplasia can only be made during life by the finding of myeloid cells in the splenic puncture with histologic evidence obtained by sternal puncture that the bone marrow has not undergone leukemic changes When these alterations are present in a patient with the picture of myelogenous leukemia in the circulating blood the diagnosis is suggested Irradiation and splenectomy are said to be of no benefit and may be harmful If one is certain of the diagnosis only symptomatic and supportive treatment is indicated The duration of life from the onset to the date of death was almost eleven years in Jackson s cases

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HODGKIN S DISEASE

Definition —Hodgkin s disease is an affection characterized by painless progressive enlargement of the lymph nodes Frequently the spleen is enlarged and the lymphoid tissue of other organs involved In the late stages fever anemia and cachexia are often important symptoms

History.—Hodgkin in 1832 described for the first time a peculiar group of cases presenting multiple swelling of lymph nodes Somewhat later similar cases were recognized in France and Germany and in 1865 Wilkes named the condition "Hodgkin s disease" A formidable list of names has been given to the disease among which are pseudoleukemia," "ademie generalized lymphadenoma, "malignant lymphoma, lymphomatosis granulomatosa malignant lymphogranuloma lymphoblastoma and chronic lymphomatosis The most common designation at the present time is Hodgkin s disease

Incidence —The ailment is comparatively common is widely spread throughout Lu rope and the Americas and is thought to be on the increase The malady attacks the young and tends to appear in the second or third decade but old age is not immune and patients have been reported up to eighty years of age Men are more likely to be affected than women

Etiology.—At present the cause of the disease remains unknown There are two principal theories as to its origin (1) that the changes in the lymphoid tissue are the result of some infection the disease thus conforming to an infectious granuloma (2) that the alterations in the lymph nodes are neoplastic in nature the disease thus belonging to the category of true tumor growths All efforts to transmit the disease to animals including apes have failed The etiology has been ascribed from time to time to a number of different bacteria Sternberg considered the disease to be a form of tuber culosis This view was upheld by Frankel and Much who found gram positive gran ular rods in the lymph nodes believed by them to be a form of tubercle bacillus Recently the disease has been ascribed to the action of avian tubercle bacilli Though the tuberculous origin of Hodgkin s disease is to some extent, still under discussion it is not an acceptable explanation to most in vestigators Other bacteria such as diph theroid bacilli described as etiologic agents have not withstood the test of time The observation that *Brucella* organisms can be cultivated from the affected lymph nodes still leaves in doubt their etiologic relation ship to the disease It is now generally thought that the encephalitis obtained by Gordon as a result of the intracerebral in oculation of emulsions of lymph nodes into rabbits is not due to a filtrable virus as he first suggested but is caused by a chemical substance derived most probably from eosin ophilic leukocytes The so called Gordon reaction is however almost never observed with any lymph nodes except those affected by Hodgkin s disease

Arguments in favor of the neoplastic origin of Hodgkin s disease have been based largely on the observation that in rare instances the process may invade neighboring tissues and assume the character of sarcoma

The view which is most widely adopted however is that Hodgkin s disease is an in fectious granuloma of unknown etiology

Morbid Anatomy —*Lymph Nodes* —The process generally makes its appearance in the cervical region on either or both sides but any group of nodes may be involved first. The order of frequency is roughly as follows cervical axillary inguinal medias tinal mesenteric and retroperitoneal At first the affected nodes are small and isolated but sooner or later they increase in size and numbers so that great collections of tumors appear in any of the locations mentioned Chainlike masses of glands sometimes ex tend from the neck into the chest and under the pectoral muscles When large groups of nodes form in the mediastinum the trachea is displaced and the esophagus and blood vessels are compressed Less often the tumors press on the spinal column or lumbar and sacral nerves rarely the cord itself is injured either by pressure or infiltration Mesenteric nodes sometimes form astonish ingly large swellings in the abdomen they have been known to obstruct the common bile duct as well as the vessels in the iliac region The tumor masses wherever found are strikingly similar Each node is round oval or slightly irregular with a smooth surface As the capsule is seldom involved the nodes are held together by loose con nective tissue The color is whitish pink semitranslucent gray or cream The con sistency varies—some of the nodes are hard others elastic or even soft In rare cases where the capsule is infiltrated the masses become much more compact

The literature contains only a few refer ences to primary enlargement of the spleen Secondary enlargement occurs in about 60 per cent of the cases Rarely if ever does the splenomegaly suggest the enormous spleen of leukemia When cut the red pulp shows many irregular pearly white or yellowish masses that vary in shape and size Infarctions also occur The liver and kidneys are less often the site of secondary deposits Any organ or structure that contains collec tions of lymphoid tissue is a target for this disease The lung is frequently invaded Growths have been described in the peri cardium pleura thymus thyroid muscles bone marrow periosteum skin central ner

vous system and gastro intestinal tract Hodgkin s disease rarely involves the tonsils a situation frequently affected in lympho sarcoma

Histology —The first well marked micro scopic changes consist of hyperplasia of the lymphoid cells with active proliferation of the germinal centers of the lymphoid fol licles There is also increased vascularity with proliferation of the reticulo endothe lium, while the reticulum itself is prominent The lymph sinuses are dilated and partially filled with cells among which there are numerous endothelial cells leukocytes, and

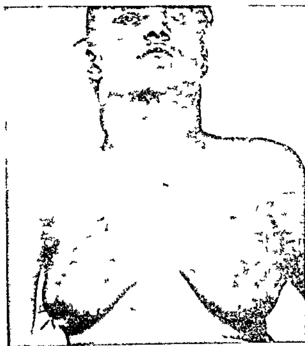


Fig 115—Hodgkin s disease in a patient thirty-six years of age Duration two and a half years In this patient the disease started with enlargement of the lymph nodes in the neck and axilla

eosinophils Karyokinetic figures are infre quently found in the endothelial cells lining the reticulum

As the disease advances the normal struc ture of the node is entirely lost and the microscopic picture shows a reticular network in the meshes of which lie lymphocytes plasma cells many eosinophils epithelioid cells and mononuclear and poly nuclear giant cells in varying proportions The most constant and striking feature is the polynucleated giant cell described by Dorothy Reed The tumor at this stage rep resents the soft type of lymphoma

In the late stage the predominating feature is the great increase in the connec tive tissue Sometimes areas of necrosis are noted and rarely hyaline degeneration is seen At this stage the tumors are much harder than in the earlier phases of the disease

Symptoms —The onset is sometimes pre ceded or accompanied by infections about the teeth or of the tonsils It remains to be proved however, that the enlargement of the cervical lymph nodes is directly associ ated with these infections

In about three fourths of the cases the disease starts with a painless enlargement of one or more groups of *superficial lymph nodes* and later pursues a fairly character istic clinical course In the remaining quarter the disease presents a much more varied clinical picture and it is possible to differentiate roughly as Ziegler has done (1) an acute form (2) a localized form (3) a generalized form, (4) a mediastinal type (5) a larval or abdominal form (6) a splenomegalic form (7) an osteoperiostitic form and to these may be added (8) a gastro intestinal form

Usually the patient first notices a gradual enlargement of the *cervical lymph nodes* The swelling is often unilateral but there commonly follows enlargement of the glands on the opposite side or the enlargement may affect both sides simultaneously In rare instances the enlargement of the axil lary or even the inguinal nodes first attracts the attention of the patient The nodes are not painful or tender nor is the skin red The swelling increases slowly and the dis ease often progresses for several months without producing constitutional symptoms *Pruritus* which sometimes appears early is often persistent and severe Occasionally the disease is limited almost entirely to the cervical region but as a rule the enlarge ment proceeds from one group of nodes to another spreading from the cervical or supraclavicular region to the axillary sub pectoral mediastinal or even retroperit oneal mesenteric and inguinal nodes The epitrochlears often escape and are seldom as large as those seen in lymphatic leukemia Glands have been known suddenly to crop up in bizarre locations such as below the clavicles over the posterior aspect of the fore-

arm or over the occiput As a rule the enlargements are not uniform in size for the nodes first affected may attain huge proportions while those involved later are comparatively small Throughout the disease the separate nodes even though in large groups may be felt as fairly well isolated masses for unless they become secondarily infected or are exposed to radium or the x ray they do not tend to adhere to the skin or surrounding tissue The *spleen* is often large but rarely reaches a great size The *liver* is usually palpable The lungs and pleurae are frequently infiltrated and large areas of solidification extend out from the roots into the lobes of the lungs The disease not infrequently affects the bone marrow and periosteum Several bones may be affected and give rise to areas of rarefaction visible in the x ray film When the vertebrae are affected the disease may extend to the spinal cord and cause paraplegia Instances are described in which the disease involved the brain Among thirty five cases of Hodgkin s disease at the Johns Hopkins Hospital the spinal cord was involved in one the cranial and sympathetic nerves in two and the cerebrum in one As the process advances the patient *loses weight* and presents a cachectic appearance The *blood pressure* is low

The enlarged regional lymph nodes may compress various structures and thus give rise to an important series of secondary symptoms Pressure on the trachea or surrounding structures causes *dyspnea dysphagia* or *laryngeal paralysis* When the brachial lumbar or sacral nerve plexuses are interfered with pain often results *Edema* of an extremity and *effusions* in the chest or peritoneal cavity may be similarly produced The fluid in sometimes bloody If the pressure is sufficient general *anasarca* may appear The clinical picture has been complicated by an obstructive jaundice Tumors sometimes compress the ureters producing bilateral pyelonephrosis or invade the brain and give rise to symptoms of tumor or diabetes insipidus

A second series of important symptoms are suggestive of infection or intoxication *Fever* is a frequent and significant accompaniment of the disease It varies considerably in its character At times it is continuous and irregular though the temperature rarely exceeds 101° F At other times there are wide daily variations The most characteristic form is the relapsing type described by Pel and Ebstein After an afebrile period lasting perhaps for weeks months or longer the temperature suddenly rises more or less abruptly to 102° or 104° F With only slight variation the fever remains high for from a few days to several weeks then recedes again to normal The afebrile period lasts for days or weeks and again the strange cycle is repeated these bouts of high temperature may occur over and over again One of our patients had ten relapses of fever during fifteen months This type of fever is more likely to appear when the mediastinal and abdominal glands are involved it must always be regarded with alarm and frequently indicates that the disease is advancing rapidly

Of all the distressing symptoms none is more bitterly complained of than *itching of the skin* It is common and often occurs early in the disease Patches of *pigment* a peculiar bronzing of the skin urticaria and crops of small erythematous nodules are sometimes present Even *ulcers* and small *superficial granulomata* have been reported We have seen patients in whom the skin looked dry but otherwise normal yet the numerous deep scratch marks bore only too eloquent evidence of the itching Herpes zoster may appear Its relation to the disease is obscure

Alterations in the blood are important though not distinctive During the early stages the total number of leukocytes may not vary from normal There is sometimes a lymphocytosis with an increase of monocytes In the later stages a polymorphonuclear leukocytosis is common Occasionally there is an eosinophilia sometimes reaching figures as high as 60 to 80 per cent In advanced stages particularly in the abdominal forms there may be a pronounced leukopenia There is rarely anemia in the early stages but as the disease progresses anemia is a distinctive feature It is usually normocytic but in some instances may be simple microcytic hypochromic microcytic or in rare cases even macrocytic in type Periods of hemolytic anemia sometimes occur accompanied by jaundice and urobi

linuria When there is widespread involvement of the bone marrow the anemia may be extreme

As the disease progresses there is continuous loss of weight with cachexia

If untreated few patients survive more than two or three years Exitus is usually due to cachexia mechanical interference with respiration or secondary infections

There are several variations from the usual clinical course of Hodgkin s disease (1) In the *acute form* death occurs within a few weeks or at most months In this form the enlargement of the lymph nodes is often remarkably widespread but not very great (2) In the *localized form* the cervical nodes are most often affected The solitary masses grow slowly for two or three years, and the disease assumes a chronic course Sooner or later, however there is an extension of the process to neighboring groups and the disease becomes more generalized (3) In the *generalized form* the disease is widespread sometimes involving practically all groups of lymph nodes and many internal organs In rare instances there is almost uniform dissemination of small lesions resembling the distribution of miliary tubercles (4) The *mediastinal type* represents one variety of the localized form in which the mediastinal nodes are especially involved The patient presents a tragic picture with all the symptoms and signs of mediastinal tumor cough dyspnea dysphagia orthopnea pain and other evidences of pressure supervene It is in this form that pulmonary lesions are most frequent The lesions usually extend from the root of the lung towards the periphery affecting one or several lobes The pleural surfaces may become involved and effusions appear When there is no enlargement of the superficial lymph nodes *it is almost impossible to make the diagnosis* The radiograph is usually of value in determining the extent of the process Hypertrophic pulmonary osteo arthropathy sometimes complicates the mediastinal form of Hodgkin s disease (5) the *larval* or *abdominal form* presents features of great importance In this type the disease is confined more or less exclusively to the thoracic or abdominal lymph nodes the superficial nodes escaping completely The symptoms are varied and indefinite Abdominal pain jaundice, diarrhea, or effusions into the pleural and abdominal cavities may occur The spleen and liver are often enlarged Fever is frequently present Some of the most pronounced examples of remittent fever are seen in this type The diagnosis is extremely difficult Cases have been mistaken in the early stages for appendicitis typhoid fever tuberculosis or liver abscess and in the later stages for malignant growths (6) In the rare *splenomegalic form* the disease is confined principally to the spleen Whether Hodgkin s disease can be entirely localized in this organ is dubious (7) Every large series of cases contains a few that show involvement of the *periosteum* and *bone marrow* It may be one of the first evidences of the disease When the bone marrow is replaced by a large amount of granulomatous tissue the anemia develops with astonishing rapidity In one case with involvement of the vertebrae there was compression of the spinal cord and paraplegia The cord itself and even the brain have been invaded (8) In the *gastro-intestinal form* large solitary or multiple tumors appear in the wall of the stomach or intestines They may occur in the absence of enlargement of the superficial lymph nodes and may result in fatal hematemesis in intestinal obstruction or in perforation

Diagnosis —The enlarged lymph nodes of Hodgkin's disease are confused most frequently with tuberculosis lymphosarcoma and follicular lymphoblastoma less often with lymphocytic leukemia Boeck s sarcoid syphilis inflammatory enlargements infectious mononucleosis and secondary carcinoma of the lymph nodes

Tuberculosis of the cervical lymph nodes is difficult to differentiate from Hodgkin s disease In tuberculosis it should be remembered that the glands are frequently tender firm and adhere one to the other and that they are likely to lie deeper in the neck than the tumors in Hodgkin s disease If the tuberculous glands have softened or are adherent to the skin or if an acute sinus has formed the diagnosis is simplified The presence of tuberculosis elsewhere in the body is an aid in arriving at a correct conclusion The tuberculin reaction is sometimes of assistance An x ray *plate often* reveals areas of calcification in tuberculous

nodes these do not occur in Hodgkin's disease

The most conclusive method of differentiating tuberculosis as well as other diseases of the lymph nodes from Hodgkin s disease is furnished by the histologic examination of an excised node It must be kept in mind however that tuberculosis may occasionally coexist with Hodgkin s disease This may lead to confusion Examination of material obtained by puncture of a lymph node is much less satisfactory and can rarely be depended upon for accurate diagnosis A positive Gordon test gives confirmatory evidence for it is obtained in about 70 per cent of cases of Hodgkin s disease

Lymphosarcoma and *follicular lymphoblastoma* simulate Hodgkin s disease even more closely than does tuberculosis Lymphosarcoma is perhaps more commonly a cause of mediastinal tumor It is less often accompanied by fever When lymphosarcoma and follicular lymphadenoma affect the cervical and submental lymph nodes the tonsils are frequently involved and greatly enlarged a condition that very rarely occurs in Hodgkin s disease In the commoner forms of lymphosarcoma the spleen is rarely if ever enlarged but in follicular lymphoblastoma involvement of the spleen is frequent and the organ may reach a great size The exact diagnosis must almost always be made from the histologic examination of an excised node

Lymphocytic leukemia should not be confounded with Hodgkin s disease the blood picture of the former disease will immediately determine the diagnosis Confusion can only arise when one is dealing with those rare cases of leukemia in which for temporary periods the leukocytes approach the normal in number and proportion The histologic changes in the lymph nodes are distinctive *Boeck s sarcoid* may occur without an eruption and without changes in the bones and under these circumstances when the lymphadenopathy is marked differentiation from Hodgkin s disease is almost impossible without the histologic examination of a lymph node *Infectious mononucleosis* can be distinguished by its acute course by the blood picture and the appearance of heterophile antibodies

There is rarely any difficulty in distinguishing the *gummatous lymph nodes* of syphilis from Hodgkin s disease The Wassermann reaction is of assistance in the diagnosis The enlarged cervical and submaxillary lymph nodes which are the seat of *metastasis from carcinoma* arising in the nasopharynx are extremely difficult to differentiate from Hodgkin s disease especially when metastatic cells are not seen When the spleen is prominently involved, there may be confusion with *Gaucher s disease*

Cases in which there is little or no enlargement of the superficial lymph nodes present the most difficult problem in diagnosis The thoracic group may be mistaken for many forms of mediastinal tumor The abdominal group has been confused with tuberculosis typhoid and where there is relapsing fever with Brucellosis The condition sometimes simulates abscess of the liver other obscure abdominal infections or carcinoma of the gastro-intestinal tract When however, there is relapsing fever enlargement of the spleen or liver progressive loss of weight and anemia with leukopenia or leukocytosis Hodgkin s disease should be considered

Prognosis —The disease tends to run a fairly steady and unfavorable course with only temporary remissions Untreated cases in collected series seldom survive longer than three years Of forty nine patients personally observed thirty four died within two years of onset It is impossible to say how efficacious treatment is but two of our patients under treatment lived for seven years one was living after fifteen years The disease progresses slowly and steadily even though the size of the nodes is controlled somewhat by the use of radium or x ray The loss of weight cachexia and anemia even in the patients treated by x ray or radium become more severe and toward the last fever is frequently present and constant Patients may die with negligible enlargement of lymph nodes Amyloid disease though rare does occur as a complication The immediate prognosis is most serious in those patients who have involvement of the mediastinal and abdominal nodes

Treatment —Surgery used to be more popular than it is at present Even though not curative it is permissible to remove large masses of the cervical nodes when the patient so wishes Any foci of infection

about teeth or tonsils should certainly be removed If surgery is employed it should without exception, be followed by radio therapy

Radium and *x-ray* are at present the most valuable therapeutic measures Although it is doubtful whether actual cures have been obtained by these procedures the course of the disease has been completely changed through their use Irradiation is most effective when the enlarged glands are localized particularly in the neck A few patients in this group are reported to have lived for fifteen to twenty years Repeated treatment by x ray or radium reduces the size of the tumor masses and thereby controls or eliminates much discomfort as well as the pain and agony that comes from pressure upon nerves, the trachea and bronchi X ray and radium are least effective in the abdominal form of the disease Bacterial vaccines preparations made from Hodgkin s disease glands and antiserum must for the present be considered experimental Arsenic has been employed for many years—it sometimes relieves the distressing pruritus and may be employed in intervals between x ray or radium treatments Preparations of iron or liver extracts have little beneficial effect upon the anemia, transfusions often give temporary help, they are sometimes followed by a remission if the fever is high

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DISEASES OF THE CARDIOVASCULAR SYSTEM

INTRODUCTION

In the light of modern physiologic concepts the heart and the entire vascular bed must be considered as a unit comprising together the circulatory system for the blood A classification of the diseases of this system which aims to be comprehensive and at the same time of practical use cannot follow rigidly the lines of structural changes or of functional derangements Nor can it adhere strictly to etiologic types for varying causative factors may produce lesions and physiologic disturbances exhibiting similar clinical patterns A ready instance is aortic regurgitation associated with congestive heart failure this combination may be the result of rheumatic fever syphilis arteriosclerosis or bacterial infection Perhaps at first glance the arrangement here followed may appear to be neither logical nor consistent But it is designed to furnish information about all of the more important diseases of the heart and blood vessels and to accomplish this purpose with a minimum of overlapping in discussion The grouping has been made according to a simple plan

In the first group are the *diseases which affect the cardiovascular system as a whole* Under this caption there has been included a discussion of the pathologic physiology of generalized circulatory failure and of cardiac pain in which particular consideration is given to the basic disturbances in function responsible for various symptoms and signs In the next group are the *diseases of the heart* divided in part according to structure and in part according to etiology The clinical features of chronic valvular heart disease are common to all types regardless of cause and are described therefore under one heading The *functional disorders of the heart* may properly be regarded as a separate group because they are not dependent for their cause upon any specific etiologic agent nor upon particular anatomic lesions Indeed some of them are occasionally observed in the absence of demonstrable cardiac pathology *Diseases of the arteries* include the manifestations of arteriosclerosis and of syphilitic aortitis and aneurysm Concerning affections of the peripheral vessels much has been learned in recent years by the use of special methods for their study Peripheral circulatory failure is taken up in a section on circulatory collapse and shock

It is hoped that this manner of presenting such a relatively large mass of material will prove helpful in promoting orderliness and clarity of thought For clear thinking leads to understanding and so to effective therapeutic procedure

ROBERT L LEVY

CLASSIFICATION OF DISEASES OF THE HEART

The difficulties in nomenclature particularly when correlating etiologic anatomic and physiologic cardiac diagnoses have made it necessary to have a standard form of classification in order that some degree of precision in nomenclature could be attained The New York Heart Association has taken the initiative and now for several years has published such a classification in the Criteria for Classification and Diagnosis of Heart Disease According to their system a complete diagnosis of heart disease must consist of three parts etiologic anatomic and physiologic

When a diagnosis of heart disease is uncertain a diagnosis of possible heart disease is made When a history is given of some condition for instance rheumatic fever hypertension or other which frequently causes heart disease and no anatomic evidence of heart disease is noted a diagnosis of potential heart disease is made

ETIOLOGIC TYPES OF HEART DISEASES

Rheumatic Heart Disease—Rheumatic fever is responsible for progressive and usually permanent structural changes in the

heart, producing a clinical picture called 'rheumatic heart disease" Reference should be made to the article on rheumatic fever (p 435) for a discussion of the incidence morbid anatomy, and symptomatology of the *active phase* of this disease In the appropriate *sections on myocarditis, chronic* cardiac valvular disease and pericarditis *structural changes* and resultant symptomatology are described Rheumatic heart *disease is essentially* a disease of the young The initial infection is most likely to occur between the ages of nine and eleven though *about 30 per cent of cases begin in the post* adolescent period It would seem that although accurate data are at present lacking the duration of life should depend to a large extent on the continued presence of active infection and the amount of damage produced On the other hand analyses of case records have shown that the number of attacks of carditis or the number of valves involved bear no relationship to the life expectancy The *average* time interval from the initial infection to the appearance of symptoms of cardiac insufficiency is about ten years and the average duration of life is about fifteen years Occasional patients however are known to have had rheumatic heart disease for as long a period as fifty years

Congenital Heart Disease—Even in childhood congenital heart disease represents only a small proportion of the heart diseases The course and prognosis depend entirely on the structural defect When little or no interference is produced with hemodynamics the condition is not incompatible with a normal life span It must be remembered however, that slight congenital defects may form the site for a superimposed subacute bacterial endocarditis See *congenital* heart disease (p 1057) and subacute bacterial endocarditis (p 1073)

Syphilitic Heart Disease—*With the exception* of a gumma of the heart which is rare syphilitic heart disease is secondary to involvement of the aorta or aortic valve and the ostia of the *coronary arteries* Reference should be made to the article on syphilis under infectious diseases (p 334) and to the article on syphilitic aortitis (p 1166) and aneurysm in the section on diseases of the arteries

Hypertensive Heart Disease—Hypertension produces secondary changes in a number of organs including *the heart* The effects of hypertension on the heart are discussed in the article on essential hypertension (p 1030) When patients begin to have *symptoms of heart failure* in this disease the prognosis is grave Fatal termination may be due to the heart itself in about two thirds of the cases This disease is frequently associated with arteriosclerotic heart disease

Arteriosclerotic Heart Disease—When *arteriosclerosis involves the coronary* arteries sufficiently to produce symptoms the condition is generally called 'arteriosclerotic heart disease (See Arteriosclerosis p 1160) Unless the course of the disease is shortened by coronary artery thrombosis or some other complication the patient may live for many years while he suffers a gradual diminution in cardiac reserve and eventually dies in congestive heart failure This disease is frequently characterized clinically by the presence of the anginal syndrome (see p 1155)

Bacterial Heart Disease—Many different organisms may produce damage to the heart *Staphylococcus Pneumococcus Gonococcus* and *Streptococcus haemolyticus* usually produce cardiac damage subsequent to a bacterial invasion of the blood stream and therefore the endocardium is chiefly affected The tubercle bacillus on the other hand produces a pericarditis (see p 1039) The *Streptococcus viridans* gives rise to a typical clinical picture which is usually designated as subacute bacterial endocarditis (see p 1073)

ARTHUR C DEGRAFF

THE PATHOLOGIC PHYSIOLOGY OF GENERALIZED CIRCULATORY FAILURE AND OF CARDIAC PAIN

An adequate blood supply is *essential for* the proper function of every organ and tissue of the body When the circulation as a whole fails as it does in heart disease or shock none of the organs of the body *functions* normally The fact that the disturbance in circulation affects every organ and *tissue is* easily *overlooked because* in many tissues a *partial loss of function* does not produce

striking clinical symptoms Interference with the function of the muscles produces a much less dramatic effect than does the same degree of disturbance in the function of the brain

Failure of the circulation as a whole occurs whenever the heart is unable to pump out sufficient blood to meet the metabolic requirements of the body This may result simply from the inability of the heart to pump out the blood which is returned to it by the great veins (heart failure) or it may result from an inadequate venous return to the heart (peripheral circulatory failure)

In the first instance—*heart failure*—symptoms and signs are produced by the following two mechanisms (1) diminished blood flow to the various tissues of the body (forward heart failure) (2) accumulation of an excess amount of blood in the various organs because the venous drainage becomes inadequate when the heart is unable to pump out the blood returned to it (backward heart failure) Although backward and forward failure must of necessity occur together since the circulation is a closed system the distinction is useful because certain symptoms result primarily from congestion while others are produced by poor tissue nutrition The observation that the basal cardiac output is normal in many of these patients does not invalidate the fact that the reduction in the cardiac output is the chief factor in the production of the symptoms of both backward and forward failure The basal cardiac output *per se* is of little significance Evidence of heart failure will be present as long as the heart is not able to respond with a normal increase in cardiac output to the demands of the patient s daily routine of living It is not possible to conclude moreover that a given disturbance in the function of an organ is not due to poor nutrition simply because the resting blood flow to the organ is normal The widespread disturbance in intermediary metabolism produced by the inability of the cardiac output to increase normally in response to the metabolic needs of the patient may cause symptoms in the presence of a normal basal blood flow

In the second type of generalized failure of the circulation—*peripheral circulatory failure*—symptoms are produced primarily by the inadequate blood supply to the tissues Though heart failure and peripheral circulatory failure have many symptoms in common they will be discussed separately

Symptoms of Heart Failure —*Dyspnea* —The patient s term for dyspnea is breathlessness or shortness of breath Dyspnea is said to be present when the patient becomes conscious of his breathing It is to be differentiated from rapid breathing (tachypnea) in which the patient may have no feeling of respiratory distress and from the deep breathing of acidosis (hyperpnea) Because dyspnea is a subjective complaint it cannot be correlated closely with objective signs of circulatory failure An anxious apprehensive and introspective patient will complain of shortness of breath when there are few objective signs of circulatory failure On the other hand a phlegmatic individual may have advanced congestive failure before he becomes conscious of shortness of breath Hence by study of the circulation one cannot determine the extent to which a given person will experience dyspnea

Normal persons have dyspnea on *unusual exertion* In a given normal subject breathlessness will appear whenever the tidal air exceeds a given portion of the vital capacity At this point the accessory muscles of respiration are brought into action and the subject becomes aware that breathing is an effort Thus dyspnea in normal persons is primarily dependent on a large increase in pulmonary ventilation In patients with diminished vital capacity less exertion will produce breathlessness because an increase in pulmonary ventilation more quickly causes the tidal air to approach the vital capacity Failure of the heart produces a decreased vital capacity by causing the lungs to become engorged inelastic and edematous As the vital capacity becomes progressively diminished smaller and smaller increases in pulmonary ventilation will cause dyspnea

The *severity* of dyspnea will depend not only on the extent of the pulmonary engorgement and the resulting encroachment on the vital capacity but also on the volume of air respired per minute A patient with a moderate degree of pulmonary engorgement may have no dyspnea at rest but when the volume of air required is increased by ex

ercise, dyspnea *may occur* *Thus the factors* which control the rate and depth of respiration play an important part in the pathogenesis of dyspnea In cardiac patients who complain of dyspnea at rest, the vital capacity is usually reduced and the ventilation is increased It was believed heretofore that this increase in ventilation rate was the result of stimulation of the respiratory center *by anoxemia or by an increase in the hydro*gen ion concentration in the region of the respiratory center because of slow cerebral blood flow

Studies of the *oxygen content the carbon* dioxide content, and the hydrogen ion concentration of the arterial blood and the blood from the internal jugular vein showed however that in cases with moderate dyspnea there was no arterial anoxemia and no measurable decrease in cerebral blood flow These observations stimulated the study of the reflex control of respiration and it was conclusively demonstrated that most of the *changes in ventilation which occurred in* normal subjects during the day were of reflex rather than chemical origin Reflexes originating from moving muscles from emotional stimuli from the lungs the great vessels and the auricles have all been shown to influence the respiratory rate In cardiac failure the increased ventilation with the resulting tendency towards alkalosis is produced by the reflex stimulation of respira*tion from the congested lungs and great* vessels

Pathogenesis of Pulmonary Congestion and Edema—There are two main factors in the pathogenesis of pulmonary congestion and edema in heart failure (a) increase in pulmonary venous pressure and (b) failure of the kidneys to excrete salt and water normally The increase in the amount of blood in the lungs with its at*tendant rise* in venous pressure occurs whenever the right ventricle pumps more blood into the pulmonary vessels than the left ventricle is able to remove (left heart failure) Such difficulty in transferring blood from the lungs may result either from interference with the filling of the left ventricle as in mitral *stenosis or from* the inability of the left ventricle to empty itself adequately with each contraction as in the heart failure produced by hypertension coronary artery disease, aortic insufficiency, and aortic stenosis It is important to remember that excess blood may accumulate in the lungs even *when the output of the left ven*tricle is normal or increased With fever exercise anemia beriberi and thyrotoxicosis signs of pulmonary engorgement may appear when the output of the left ventricle is still above the normal basal level The explanation is that in such cases the output of the left ventricle though 'normal is lagging behind that of the right ventricle

In massive infarcts of the left ventricle in a patient without previous evidence of congestive failure the increase in pulmonary venous pressure appears to be the only factor operative in producing the pulmonary engorgement and edema The loss of fluid into the lungs causes a moderate degree of hemoconcentration The right ventricle pumps blood into the pulmonary vessels which the infarcted left ventricle is unable to remove

When heart failure develops more slowly as usually happens and when the left ventricle is more nearly capable of keeping up with the right ventricle a second and important factor becomes operative in the development of the pulmonary congestion—namely the tendency for a person with a failing heart to retain salt and water *The* excess normal saline leaves the blood stream and is deposited in the tissues in areas where *the tissue pressure is low or where the* venous and capillary pressures are increased This problem will be discussed in more detail in the section on *edema* In these cases even a slight increase in pulmonary venous pressure because of heart failure is sufficient to cause a considerable portion of the retained water to *accumulate in the* lungs

Dyspnea on *exertion* is the presenting symptom in most cases of congestive failure The patient discovers that he becomes short of breath after an effort which formerly caused no discomfort The first objective sign of this failure is usually a decrease in vital capacity *followed by an increase* in the pulmonary circulation time Moist rales at the bases are frequently present It cannot be emphasized too strongly that in the absence of the anxiety syndrome dyspnea in heart disease always means pulmonary congestion and edema regardless of the physical

findings in the lungs In certain patients the edema is primarily pericapillary and not intra alveolar In these cases intense dyspnea and pulmonary edema may be present even though auscultation of the lungs reveals no rales

Summary—Dyspnea in heart disease is produced by the changes in the lungs which result from interference with the venous drainage of the lungs and from the tendency of the cardiac patient to retain excess salt and water Reflex stimulation from the congested lungs plays an important role in the mechanism of dyspnea The pulmonary changes producing the dyspnea are the result of a combination of backward heart failure (increased venous pressure in the pulmonary veins because of mitral stenosis or failure of the left ventricle) and of failure of the kidneys to excrete salt and water normally The backward failure in the lungs causes a large amount of the saline retained by the kidneys to be deposited in the lungs It is obvious that anything which further decreases the vital capacity or which by reflex action increases the ventilation rate will increase the dyspnea Hydrothorax pulmonary infarcts and pneumonia all increase the dyspnea of cardiac failure through both of the above mechanisms Fright anxiety and pain precipitate attacks of dyspnea in cardiac patients with a lowered vital capacity primarily by a reflex increase in the ventilation

Orthopnea—Orthopnea is a more advanced stage of dyspnea in which the patient refuses to lie flat in bed because when he assumes the horizontal position his difficulty in breathing increases In heart disease dyspnea at rest is a relative state With the trunk raised above a given angle the patient may have no dyspnea When the trunk is below that angle dyspnea will occur Orthopnea like dyspnea is a subjective sensation and so as in dyspnea there is no close correlation between the degree of orthopnea and the objective signs of circulatory failure The reflex sensitivity of the central nervous system of the individual patient determines at what level of pulmonary congestion and edema orthopnea first appears In advanced heart failure with disturbance in consciousness the patient may have less orthopnea despite increasing pulmonary edema Because orthopnea is a subjective sensation an unconscious patient cannot be orthopneic

It was believed formerly that the assumption of the upright position decreased the dyspnea because it relieved the venous congestion supposed to be present in the brain Clinical investigation showed that this hypothesis was untenable because in many patients with orthopnea the venous pressure is normal and because marked elevation of the venous pressure in the brain in cases of superior mediastinal obstruction does not cause orthopnea There is no constant change in arterial oxygen saturation when the orthopneic patient is lowered to a position where he complains of dyspnea Estimation of the cerebral blood flow by determination of the oxygen content of arterial blood and of blood from the internal jugular vein reveals no constant change in cerebral blood flow with change in position Thus there is no evidence that the circulation to the medullary centers is improved when the patient is upright

Orthopnea depends primarily on the active stimulation of the pulmonary reflexes resulting from congestion of the lungs As the trunk is lowered the venous pressure in the lower part of the body is decreased This causes a redistribution of blood with a momentary rise in the output of the right ventricle and an increase in pulmonary engorgement With it comes a tendency towards reduction of vital capacity (In addition the vital capacity may be slightly decreased in the recumbent position because of the upward movement of an enlarged liver) This sequence of events produces a reflex rise in pulmonary ventilation and the patient becomes dyspneic Even in normal subjects the vital capacity is somewhat greater in the upright position than in the recumbent position Hamilton and Morgan observed that the vital capacity of normal subjects in the recumbent position was increased when blood was pooled by the application of tourniquets to the four extremities After the limbs were congested by tourniquets change in posture caused little change in vital capacity These data suggest that even in normal persons the blood volume in the lungs is appreciably increased when the subject lies down

While factors other than those enumerated eventually may be shown to be important in producing a slight lowering of the vital capacity, clinical observations leave little doubt that reflex stimulation from the engorged and edematous lungs is the chief factor in the orthopnea of cardiac failure It is a common observation that the administration of morphine will allow a cardiac patient to rest comfortably in a position he had previously been unable to endure because of dyspnea Reducing the sensitivity of the central nervous system in these patients relieves the dyspnea without producing any measurable change in the circulation

Paroxysmal Dyspnea and Cardiac Asthma.—Attacks of shortness of breath which come on suddenly—often while the patient is asleep—occur frequently in patients with cardiac failure from hypertension coronary artery disease aortic insufficiency and aortic stenosis, all diseases which cause strain or injury to the left ventricle Although these attacks of dyspnea frequently occur in patients who are already incapacitated by chronic congestive failure they may occur at night in patients who during the day seem to have a fairly good cardiac reserve and who are able to carry on their daily work The stroke and minute output of the left ventricle, the velocity of the venous blood flow, and the oxygen difference between the arterial and venous blood obtained from the femoral vessels are all essentially normal In many cases the liver is not palpable and there is no pitting edema In some patients, however the cardiac output is diminished Even though the peripheral circulation appears normal at rest the lungs show signs of congestion The mean velocity of pulmonary blood flow is usually decreased On x ray examination the hilar shadows are enlarged with a fan like radiation towards the periphery Moist rales are usually though not always, present The vital capacity is diminished and the volume of the residual air is increased

During the attack the patient sits up or stands up The skin becomes ashen the small veins are collapsed and there is profuse sweating The respiratory mid position of the thorax becomes elevated and there is a tendency for the chest to become fixed in the forced inspiratory position Both inspiratory and expiratory distress are usually present Asthmatic wheezes and moist rales are frequently audible In some cases only moist rales are heard In certain patients in spite of intense dyspnea there are no rales Tachycardia is invariably present Embryocardia and gallop rhythm are common The pulmonary second sound is accentuated The peripheral circulation shows variable changes The volume output of the heart either remains the same or decreases The arterial pressure is usually elevated, the venous pressure either does not change or shows a moderate increase The oxygen saturation of the arterial blood may show little or no decrease If the bronchial constriction is marked or if severe pulmonary edema develops the oxygen saturation may be markedly decreased The volume of blood flowing through the lungs either shows no change or decreases the mean velocity is decreased Diminished velocity in the presence of a relatively normal volume of blood flowing through the lungs indicates that the cross section area of the pulmonary vascular bed is increased and that the lungs contain more blood during the attack

The above data indicate that the paroxysm of dyspnea is caused by the sudden trapping of a few hundred cubic centimeters of blood in lungs which are already moderately congested Because normal function has been impaired by disease the left ventricle is unable to increase its output sharply enough to clear the lungs This engorgement then is produced by a temporary imbalance between the outputs of the right and left ventricles wherein the output of the right ventricle exceeds that of the left In a short time the balance between the two ventricular outputs is restored but the left ventricle is unable to do more than keep up with the right ventricle It does not have enough reserve strength to remove the excess blood from the lungs This excess blood reduces the efficiency of the lungs by decreasing the vital capacity and by decreasing the pulmonary elasticity These changes in the lungs cause a reflex increase in pulmonary ventilation

If the bronchi respond to the pulmonary congestion by spasm or if the lumina of the bronchi are narrowed by edema of the bron

chial mucosa asthmatic wheezes and groans will be present Bronchial wheezes are more apt to develop if the patient has a history of repeated attacks of bronchitis or if he has chronic lung disease such as emphysema or bronchiectasis In some patients the edema that develops is pericapillary rather than intra alveolar in which case there are no rales In any case the fundamental mechanism of the attack—namely, sudden pulmonary engorgement with a left ventricle incapable of removing the blood—is the same

Paroxysmal attacks of dyspnea usually occur at night In patients who have orthopnea the attack is frequently brought on by sliding into the horizontal position while asleep In patients who are ambulatory the assumption of the horizontal position at rest tends to bring a redistribution of the blood and fluid in the body When the patient lies down blood is shifted from the abdomen and the upper and lower extremities to the lungs and to the great veins of the thorax This redistribution of blood is one of the factors which cause the vital capacity of normal subjects to be less in the horizontal than in the upright position Although there may be no pitting edema in many of these patients who have paroxysmal nocturnal dyspnea the quantity of extracellular fluid is increased During the day this fluid accumulates mainly in the lower part of the body because of the high venous and capillary pressures caused by the upright position When the patient lies down the venous pressure in the lower part of the body is decreased and excess fluid enters the blood stream causing an increase in blood volume If the pulmonary venous pressure is slightly elevated much of the fluid is deposited in the lungs causing edema and further reduction in vital capacity The stage is now set and any stimulus which causes the patient to increase the output of the right ventricle for a short time will precipitate the paroxysms of dyspnea Coughing noise nightmares and a distended bladder often act as the trigger mechanisms The hyperpnea phase of Cheyne Stokes breathing also frequently precipitates an attack

Periodic Breathing—(Cheyne-Stokes Respiration) —In many patients with cardiac failure the regular sequence of respiratory movements is replaced by alternating periods of underbreathing and overbreathing As the condition becomes more marked apnea and hyperpnea occur The periods of apnea may last from 15 to 60 seconds The apneic period is terminated by respirations of a gradually increasing depth until marked hyperpnea occurs The depth of the respirations then gradually decreases until the next period of apnea begins During the period of apnea the patient is frequently drowsy sleepy or stuporous As the hyperpnea begins he frequently arouses moves about restlessly and not infrequently moans or cries out He frequently complains of dyspnea and if he has fallen back on the pillow he will sit upright The hyperpnea of Cheyne Stokes breathing is often the trigger mechanism which precipitates an attack of cardiac asthma

Periodic breathing in heart failure is the result of incoordination of the nervous and chemical factors which normally control respiration The exact nature of the incoordination has not been determined This type of respiration may occur in normal sleeping babies It may also be seen in patients after cerebral accidents or trauma to the central nervous system or in patients with meningitis uremia or other forms of coma In all of these conditions the sensitivity of the respiratory center is depressed In sleep the depression is physiologic in cardiac failure it is the result of the inability of the heart to maintain the normal cardiac output and to nourish the brain properly That cerebral metabolism is disturbed in these patients is shown by their restlessness the narrowing of the field of consciousness and the difficulty in fixing attention

The lowering of the blood flow to the brain because of decreased cardiac output is not the only factor responsible for depression of the respiratory center Changes in cerebral blood flow because of local vascular disease play an important part In addition changes in the cerebral metabolism because of decreased blood supply to the liver kidneys and all other tissues are probably important The respiratory center becomes insensitive to the normal concentration of carbon dioxide and apnea results When respiration ceases the carbon dioxide concentration of the arterial blood steadily in

creases until finally the sluggish respiratory center is stimulated and hyperpnea occurs The carbon dioxide concentration continues to fluctuate and the patient suffers alternately from apnea and hyperpnea

Periodic breathing occurs in normal subjects at high altitudes Both a decrease in oxygen tension and a decrease in carbon dioxide tension of the arterial blood appear to be operative The fall in carbon dioxide tension is secondary to the stimulation of respiration resulting from the anoxemia Whether the anoxemia affects the respiratory center directly or whether it works through peripheral receptors such as the carotid sinus is not clear The administration of carbon dioxide invariably stops the periodic respiration The administration of oxygen frequently makes the periodic breathing less marked and occasionally stops it

In cardiac failure there is usually a tendency for the carbon dioxide content of the arterial blood to be lowered because of the reflex stimulation of respiration from the engorged lungs Both this tendency towards alkalosis and the depression of the respiratory center appear to be important in producing the periodic breathing The interaction between these two factors probably accounts for the effect of sleep and morphine on Cheyne Stokes breathing In cardiac failure periodic breathing frequently begins as the patient is going to sleep Presumably the physiologic depression of the respiratory center combined with the over breathing produced by the reflexes from the congested lungs initiates the periodic breathing As sleep deepens the ventilation decreases the carbon dioxide content of the blood tends to increase and the periodic breathing may cease The effect of morphine is variable In large doses it depresses the respiratory center and causes a marked prolongation of the periods of apnea and hyperpnea In smaller doses it may cause the respirations to be more regular This is probably due to the fact that smaller doses decrease the ventilation rate and reduce the tendency towards alkalosis but are not powerful enough to cause any marked depression of the respiratory center

When periodic breathing is marked the oxygen content of the arterial blood will be decreased during the apneic phase and the carbon dioxide content of the arterial blood will be increased These changes in the blood gases and corresponding changes in hydrogen ion concentration are the result rather than the cause of the periodic breathing Once the periods of apnea and hyperpnea have begun, the changes in hydrogen ion concentration are probably important in explaining the variations in depth of respirations during the hyperpneic period

Periodic breathing in cardiac failure usually results from a combination of forward and backward failure of the left ventricle The reflex overbreathing and pulmonary congestion (backward and forward failure) and the depression of the respiratory center (forward failure) are all factors of importance

Edema—Failure of the heart characteristically results in the retention of water and salt The patient may retain from ten to twenty pounds of water before there is any objective sign of the increased extracellular fluid (sub clinical edema) As the process continues the patient notices that his shoes are tight and that his ankles are swollen in the evening On arising in the morning the swelling has disappeared In the more advanced stages pitting edema is present continually and eventually the scrotum and abdominal wall become waterlogged If the patient is confined to his bed edema of the back and sacral regions may be more extensive than that of the lower extremities Hydrothorax occurs usually first on the right and later bilaterally Ascites may develop

Edema of the lower extremities produces a feeling of heaviness but does not cause actual pain The skin may become so tightly swollen that the body cannot nourish it Therefore low grade cellulitis is not uncommon At times the pressure of the extracellular fluid becomes so great that the skin ruptures and fluid drains freely from the part Hydrothorax produces dyspnea by lowering the vital capacity Less frequently ascites is a factor in the production of dyspnea It is possible that a portion of the anorexia and nausea occurring in congestive failure may be produced by the excess fluid in the tissues of the abdominal viscera The generalized retention of water has already

been discussed as an important factor in the production of dyspnea

The *mechanism* of cardiac edema has never been satisfactorily explained For merly the edema was thought to be a mani festation of backward heart failure (failure of the right ventricle) It is well known that elevation of the venous pressure pro duces edema and it was assumed that the edema in cardiac failure was secondary to the rise in venous pressure Recent studies have demonstrated that in patients with chronic congestive failure edema is present before there is a measurable rise in the rest ing venous pressure The possibility that the venous pressure may be abnormal dur ing activity and thus account for the fail ure of the kidney to excrete salt and water normally has not been excluded

The available data suggest that the re tention of the sodium ion by the kidney is the fundamental cause of cardiac edema The retention of water is secondary to the retention of the sodium ion It is not clear whether this disturbance in renal function results from chronic passive congestion or from a disturbance in renal blood flow be cause of the inability of the heart to main tain an adequate circulation while the pa tient is active As the salt and water reten tion becomes more marked the plasma vol ume gradually increases the quantity of circulating protein rises and finally there is an increase in the resting systemic ven ous pressure The retained salt and water are distributed throughout the body in areas where the capillary pressure is high or where the tissue pressure is low During the day when the patient is upright the high ven ous and capillary pressures produced by gravity cause most of the excess fluid to accumulate in the portion of the body be low the level of the heart When the pa tient lies down the venous and capillary pressures become more nearly equal through out the body *This results* in a redistribu tion of the excess fluid over the body in general If the pulmonary venous pressure is increased due to left ventricular failure much of the excess fluid is deposited in the lungs The remainder is lodged in areas where the tissue pressure is low

In the above discussion a distinction is made between the generalized rise in ven ous pressure which occurs in cardiac failure and the local rise in venous pressure which is produced by placing a part below the level of the heart The rise in pressure throughout the venous system is produced by the large blood volume which distends the venous bed At least in some patients the elevated venous pressure is the *result* rather than the cause of the edema The local increases in venous and capillary pres- sures produced by postural effects are of primary importance in determining the dis tribution of the excess saline retained by the kidney

The low protein content of cardiac edema fluid shows that neither increased capillary permeability nor lymphatic blockage plays a significant part in the mechanism of car- diac edema Even in patients with marked lack of arterial oxygen saturation capillary permeability seems to be normal Lowering of the serum protein concentration always predisposes to the formation of edema This is a secondary factor in certain patients with congestive failure

Cough—Cough and expectoration are fre- quent complaints in patients with cardiac failure The cough is produced by a reflex from the congested lungs and bronchi Less commonly cough results from pressure of an aneurysm on the trachea bronchi or recurrent laryngeal nerve Rarely marked enlargement of the left auricle may pro duce cough by pressure on the bronchi The cough produced by congestive failure may be severe enough to interfere with sleep and it is frequently the trigger mechanism which precipitates an acute attack of nocturnal dyspnea

Hemoptysis—Bleeding from the lung or bronchial mucosa occurs frequently in heart failure In mitral stenosis bleeding from the dilated pulmonary vessels is common and may occasionally be fatal Bleeding from congested vessels in the bronchial mucosa is *seen in severe heart failure* from any cause Bloody sputum is a frequent symptom of pulmonary infarction In severe pulmonary edema caused by left ventricular failure bloody froth may pour from the bronchial tree

Weight Loss—Patients with chronic con gestive failure suffer from a gradual loss of tissue which is frequently unnoticed because

of the accumulation of edema If failure persists for a long period of time, the cachexia may become as marked as that produced by advanced malignancy The loss of weight is a manifestation primarily of forward heart failure The heart does not pump enough blood to nourish the tissues properly The observations of Gross on the nutritional state of children before and after ligation of a patent ductus are particularly significant These studies show that physical development was retarded by poor peripheral blood flow even in the absence of the usual signs of congestive failure When the peripheral blood flow was increased by obliteration of the patent ductus arteriosus, growth was accelerated

Anorexia Nausea, and Vomiting—Gastro intestinal symptoms are common in congestive failure and they may originate in a number of ways The reversible medullary reflex interrelationship existing between the heart and stomach makes it possible for either stomach or heart to be the precipitating agent Irritation of the gastric mucosa may produce reflex heart block or auricular standstill Reflexes arising in the heart from myocardial infarction or from digitalis fixed in the heart may cause contractions of the stomach with reverse peristalsis nausea and vomiting Congestion of the abdominal viscera themselves may cause nausea and vomiting Central stimulation of the reflex pathways producing vomiting may occur when the metabolism of the brain is disturbed Hiccough is present at times in patients with myocardial infarction and is usually a symptom of serious prognostic significance

Abdominal Pain—Pain in the right upper quadrant is a common symptom of congestive failure The pain may be present at rest or it may occur only on exertion In certain patients the right upper quadrant pain and tenderness occur while the venous pressure is still normal and there is no pitting edema Palpation usually reveals an enlarged tender liver Acute enlargement of the liver generally causes severe pain because of stretching of the capsule Once the capsule has been stretched there may be marked enlargement of the liver with little discomfort Engorgement of the liver as the result of increased blood volume and of increased venous pressure is undoubtedly important in causing such pain and enlargement of the liver The lack of close correlation between the height of the venous pressure and the degree of liver enlargement indicates that in addition to this engorgement one or more factors not yet understood are also operative

Cerebral Symptoms—Symptoms of cerebral dysfunction are very common in heart disease although they do not usually appear until the patient has reached the stage when dyspnea is present at rest Pulmonary congestion from poor venous drainage of the lungs and from retention of salt and water usually is present before the cardiac output decreases to a degree sufficient to produce a significant change in the metabolism of the brain As the heart continues to fail however the cardiac output even at rest becomes inadequate to nourish the brain properly and irritability restlessness and difficulty in fixing attention develop The eventual sequence is that of stupor coma and death These symptoms of inadequate cerebral metabolism are often part of the clinical picture of congestive failure during the last few days or weeks of life A change in personality a mild delirium or mental depression is frequently the presenting symptom in the circulatory failure produced by myocardial infarction It is probable that the changes in cerebral metabolism caused by heart failure have a mechanism more complicated than simple reduction of the blood supply to the brain It seems evident that there must be widespread disorders of intermediary metabolism produced by the decreased blood supply to the liver endocrine glands gastro intestinal tract and all other organs of the body Such lack of proper function of other organs may well have a secondary effect on cerebral metabolism The cerebral symptoms are accentuated if the oxygen saturation of the arterial blood is decreased because of severe pulmonary changes either secondary to or independent of the congestive failure

Palpitation—Persons—both sick and well—complain frequently of the fact that they are conscious of the beating of their hearts On the one hand this may be due simply to increased awareness of normal physiologic variations in cardiac output

(anxiety state) On the other hand it may be the result either of changes in stroke volume or rate of the heart or of cardiac enlargement Anything which increases the stroke output of the heart will cause the patient to complain of palpitation unless his attention is centered elsewhere For example the beat after an extrasystole is noticed because a longer period of diastolic filling causes the stroke volume of this beat to increase Exercise excitement thyrotoxicosis and anemia cause palpitation by increase in stroke volume and minute output of the heart Increases in heart rate without a rise in the minute volume output of the heart are less apt to cause palpitation Any change from the usual rhythm may cause awareness of the heart beat When the heart is enlarged palpitation is more likely to be experienced because the heart lies closer to the chest wall Both normal subjects and patients with heart disease commonly complain of palpitation when lying quietly on the left side This position causes the apex impulse to shift nearer the chest wall

Anxiety State in Persons with Heart Disease—The layman knows that proper cardiac function is necessary to sustain life and that heart disease is a common cause of death The diagnosis of heart disease offers such a threat to the security of the individual that it is safe for the physician to assume that anxiety is present whenever the patient knows or suspects that he has heart disease The degree and manner in which this anxiety is expressed will depend on the personality structure of the individual person Failure of the physician to differentiate between the symptoms of anxiety and those of heart failure frequently causes invalidism for years before the circulation actually becomes inadequate

Persons who have real or imaginary heart disease without any circulatory failure are apt to interpret many normal physiologic phenomena as evidence of heart failure The slight feeling of giddiness which is produced by changing suddenly from the recumbent to the upright position and the palpitation which is produced by excitement fear or exercise are frequently interpreted by the patient as signs of circulatory failure Hyperventilation is easily produced by anxiety and may lead to the mistaken diagnosis of paroxysmal dyspnea due to early congestive failure The following sequence of events is common A patient with compensated heart disease is suddenly aroused from sleep by a noise or a nightmare This produces an increase in pulmonary ventilation At the same time the patient notices palpitation because of the increase in cardiac output from the sudden awakening The palpitation is interpreted as a symptom of the circulatory failure and the resulting anxiety causes a further increase in pulmonary ventilation The rise in pulmonary ventilation without an increase in muscular activity produces alkalosis by lowering the carbon dioxide content of the arterial blood The alkalosis alters the cerebral metabolism and the patient feels giddy and uncertain The hands and feet become cold and the extremities tingle Rarely tetany develops These cerebral symptoms are interpreted as symptoms of heart failure and sudden death is feared The patient becomes conscious also of the increase in respiratory rate and this again is interpreted as heart failure

In taking the history one should always ask whether the attacks of dyspnea suspected of being caused by heart disease are accompanied by faintness giddiness sense of unreality loss of consciousness coldness of the hands and feet and tingling sensations around the mouth or down the extremities Whenever the symptoms appear more severe than is compatible with the objective signs of heart disease it is advisable to determine whether the sensations produced by voluntary hyperventilation are similar to those described by the patient as shortness of breath

Symptoms of Peripheral Circulatory Failure—The symptoms of peripheral circulatory failure are caused chiefly by the marked decrease in cardiac output which results from the ineffective filling of the heart because of a decrease in venous return Inadequate filling of the circulatory system is responsible for such a decrease in venous return and it may be due to either one of two circulatory disturbances (1) diminished blood volume (hemorrhage trauma or burns) (2) increase in size of the circulatory bed so that the normal blood volume is inadequate to fill the dilated bed (postural fainting sodium nitrite collapse) The

clinical syndrome produced by a transient failure of the venous return is called collapse or primary shock, that produced by a more prolonged failure of the venous return *is called shock or secondary shock* In peripheral circulatory failure there is pallor of the skin, coldness of the extremities cold perspiration, weak and thready pulse narrowing of the field of consciousness restlessness, low arterial pressure narrow pulse pressure and constricted veins All of these signs are secondary to the fall in cardiac output They are also seen in varying degrees in patients with heart failure In heart disease however the decrease in cardiac output is caused by cardiac weakness rather than by a decreased venous return

Syncope —Loss of consciousness from a *transient decrease in cerebral blood flow* is called syncope The decrease in cerebral blood flow may result from cardiac standstill or from a diminished venous return to the heart The *cardiac standstill* (Adams Stokes syndrome) may be caused by heart block because of disease of the bundle of His or by overactivity of certain vagal reflexes whose afferent limb may originate in any organ of the body Afferent impulses from the carotid sinus the heart itself any portion of the gastro intestinal tract the pleura the peritoneum the gallbladder the uterus the vagina, or the prostate may produce sino auricular standstill or auriculoventricular block by way of the vagus nerves

Diminished venous return to the heart may result from pooling of blood in the lower part of the body as for example in motionless standing or it may result from peripheral vasodilatation due to reflex stimulation from the carotid sinus or various other afferent areas such as the pleura peritoneum or mesentery When widespread disease of the sympathetic nervous system is present, syncope may occur in the upright position because of failure of the normal reflex vasoconstrictor response to standing (postural hypotension) Less commonly syncope occurs because of the decrease in cardiac output from marked tachycardia

Reflex hyperventilation is a frequent cause of syncope The alkalosis caused by the loss of carbon dioxide from the arterial blood either interferes with cerebral metabolism directly or produces its effect by a slowing of the cerebral blood flow The combination of emotional hyperventilation and the decreased venous return to the heart because of the upright position is responsible for many attacks of benign fainting Neurogenic stimuli which cause a reflex fall in blood pressure are also probably important in explaining the ordinary fainting attack

Certain *afferent stimuli* apparently cause unconsciousness by direct action on the central nervous system Stimulation of the *carotid sinus* in certain individuals causes unconsciousness without any slowing of the heart or fall in arterial pressure (central type of carotid sinus response) As far as can be determined by studies of the oxygen content of the blood from the carotid artery and the internal jugular vein, this type of syncope *is not accompanied by a change in* cerebral blood flow

Any severe attack of *pulmonary congestion* from heart disease may be accompanied by unconsciousness Syncope is seen most frequently with aortic stenosis but it has been described with pulmonary congestion resulting from coronary artery disease mitral stenosis and aortic insufficiency It appears that the suddenness and severity of the attack of failure is more important than the type of heart disease The mechanism of these attacks of syncope has not been established They may have a varied etiology Reflex cardiac standstill transient arrhythmia cerebral anoxemia from a sudden inability of the heart to maintain an adequate cardiac output hyperventilation caused by the severe pulmonary congestion may each play an important role in certain cases

Shock Syndrome in Heart Disease—A marked decrease in cardiac output causes a clinical syndrome resembling that described as peripheral circulatory failure or shock Narrowing of the field of consciousness restlessness stupor pallor cold sweat, constricted veins in the extremities low arterial pressure narrow pulse pressure weak and thready pulse are frequently seen in patients with heart disease It is important to realize that though these signs are identical with those found in shock they are the result of heart failure rather than peripheral circulatory failure The picture may develop in a normal heart which is

unable to pump blood successfully because of marked tachycardia In paroxysmal auricular tachycardia auricular flutter or rapid auricular fibrillation the cardiac output may be markedly decreased because the period of diastole has been shortened until there is not sufficient time for proper ventricular filling Interference with proper ventricular filling likewise causes the shock syndrome to develop in pericardial tamponade and to a lesser degree in constrictive pericarditis

In the last few hours or days of life most patients with congestive failure develop the symptoms and signs of a marked decrease in cardiac output These patients with chronic congestive failure usually have a large blood volume and high venous pressure so that it is obvious that the decrease in cardiac output results not from a decrease in venous return but from the inability of the heart to pump blood in the presence of an adequate venous return Patients with a massive myocardial infarct who have never had congestive failure develop the clinical syndrome of shock without distention of the neck veins They tend to show hemoconcentration rather than the increase in blood volume seen in chronic congestive failure Roentgenograms of the lungs however show marked pulmonary congestion and edema The pathologic findings in the heart help to explain the clinical picture The area of infarction usually involves the left ventricle primarily The right ventricle pumps blood into the lungs but the infarcted left ventricle is not able to pump out the blood it receives Sufficient fluid is lost into the lungs to cause some degree of hemoconcentration The lungs become intensely engorged as the output of the left ventricle decreases The decrease in output of the left ventricle causes the clinical syndrome of shock

In summary heart disease may produce the *clinical* picture that is described as characteristic of peripheral circulatory failure or of shock It is clear however that this failure is not peripheral in origin It is caused by the inability of the heart to pump blood not by an inadequate venous return The term "cardiac shock is used only to describe the clinical appearance of the patient It has no physiologic connotation

Cardiac Pain —When the metabolism of the heart muscle exceeds the available blood supply tissue metabolites accumulate and cause pain This does not occur in a normal subject because the extra metabolites produced by an increase in the work of the heart cause coronary vasodilatation with a resultant increase in coronary blood flow In the normal subject dyspnea or fatigue has limited activity before the functional reserve of the coronary circulation is exhausted An inadequate coronary circulation may develop in any one of three ways (1) narrowing or obstruction of the coronary vessels from arteriosclerosis or obstruction of the ostia of the coronary arteries by syphilitic aortitis (2) cardiac hypertrophy without a corresponding increase in the number of capillaries so that there are fewer blood vessels per unit area of tissue (3) interference with the coronary circulation because of the altered hemodynamics present in aortic insufficiency aortic stenosis and in certain cases of advanced mitral stenosis

When coronary insufficiency first begins to develop there are no symptoms at rest because the resting coronary blood flow is normal and metabolites are removed in the normal way from the heart muscle Pain occurs when the work of the heart is increased by exercise excitement eating anemia or thyrotoxicosis In patients with coronary artery disease the increase in the work of the heart causes dilatation in many portions of the coronary vessels just as it does in normal subjects This vasodilatation however is ineffective if there are fixed obstructions to the coronary tree or if there are too few blood vessels to nourish properly the hypertrophied muscle fibers or if the dynamics of the circulation are so altered that coronary vasodilatation does not cause the normal increase in coronary blood flow The coronary blood flow is then inadequate for the metabolic needs of the muscle and pain develops When the work of the heart is reduced by rest the coronary circulation is again sufficient for the metabolic needs of the heart and the pain disappears As the insufficiency of the coronary circulation becomes more marked a smaller increase in cardiac work will be capable of producing pain And finally pain may be present at rest

Epinephrine produces coronary vasodilatation in normal subjects but at the same time it increases the work of the heart In patients with coronary artery disease the administration of epinephrine causes pain because the heart reacts with an increase in cardiac output, although the sclerotic narrowed areas in the coronary vessels are not capable of the normal physiologic vasodilatation in response to epinephrine which would compensate for the increase in cardiac work This explains the apparent paradox that a drug which produces coronary vasodilatation also produces cardiac pain

Occlusion of a coronary artery does not in itself produce pain If sufficient collateral circulation has been established before the vessel is occluded so that the heart muscle is properly nourished there will be no pain Indeed several coronary branches are often occluded before the insufficiency of the coronary circulation becomes marked enough to produce pain on exertion Myocardial infarction occurs when the coronary circulation is not able to nourish the muscle at rest This produces prolonged pain which is not relieved by rest and it is accompanied by the signs of muscle necrosis namely fever leukocytosis and an increase in sedimentation rate Not infrequently in patients with angina pectoris acute insufficiency of the coronary circulation may develop without actual myocardial infarction Under these circumstances the pain is prolonged but there are no signs of muscle necrosis These attacks of acute coronary insufficiency are produced in three ways (1) occlusion of an additional branch of a coronary vessel so that the coronary circulation —though still adequate enough to keep the muscle alive—is incapable of preventing the accumulation of metabolites which produce pain (2) prolonged increase in the work of the heart such as occurs after the administration of epinephrine (3) interference with the hemodynamics of the circulation as a whole as in pulmonary infarction The pain produced by insufficiency of the coronary circulation is typically substernal rather than precordial In a classical case it radiates down the ulnar aspect of one or both arms or up to the neck This radiation is apt to be modified if there is inflammation in other parts of the body If there is an abscessed tooth radiation to the jaw is frequent If there is inflammation around the kidney pain may radiate to the costovertebral angle

Patients with acute pericarditis or acute rheumatic myocarditis frequently complain of dull precordial pain A constant dull precordial ache with tenderness on palpation beneath one or both breasts is a common symptom also in anxious persons who have no heart disease

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ESSENTIAL HYPERTENSION

Definition —*Essential hypertension* is a term employed to indicate the existence of abnormally high systolic and diastolic arterial blood pressure in individuals who have neither inflammatory kidney disease urinary tract obstruction or other disorders which are known to result in elevation of the blood pressure It is clear according to this definition that the term can be used correctly in diagnosis only after known causes of hypertension have been excluded It should be emphasized that in essential hypertension we may be dealing really with a number of different disorders even though the above restrictions in the use of the term are observed However if this is the case these disorders have in common (1) *elevation* of the blood pressure and (2) the absence of either primary parenchymal renal disease or other conditions which are known to produce hypertension Until more is known concerning etiology and pathogenesis it serves a useful purpose to continue to employ the term essential hypertension

History —Hypertension was formerly regarded as always being an expression of either Bright's disease (nephritis) or arteriosclerosis In 1874 Mahomed described the "prealbuminuric stage of Bright's disease" a term indicating that hypertension may precede frank nephritis but not disassociating the two Von Basch 1894 recognized that hypertension may exist in the absence of nephritis and demonstrable arteriosclerosis and attributed it when present under these circumstances to latent arteriosclerosis" Allbutt 1896 differentiated hypertension ("hyperpiesia") from Bright's disease and senile arteriosclerosis Huchard 1899 also recognized hypertension in the absence of Bright's disease and, to emphasize its importance in the etiology of arteriosclerosis called it presclerosis" Hypertensive cardiovascular disease" was the designation used by Theodore Janeway in 1913 and it became widely accepted at the time Frank in 1911 introduced the term essential hypertension" Volhard and Fahr (1914) and Keith Wagener and Kernohan (1928) have especially directed attention to cases of essential hypertension which are characterized by kidney involvement and a rapidly progressive fatal course—"malignant nephrosclerosis or "malignant hypertension" in contrast to the commoner "benign" disorder The importance of cerebral vascular spasm in the production of symptoms was emphasized by Pal (1905) and discussed in detail by Oppenheimer and Fishberg (1928)

Etiology and Pathogenesis —The high incidence of essential hypertension is indicated by Janeway's figures on a large group of private patients The systolic blood pressure was over 165 mm in 11 per cent This was a result of essential hypertension in the vast majority of instances Hypertension was present in somewhat less than 2 per cent of more than 600 000 candidates for life insurance (Frost Knight) Fahr estimates that hypertension or its sequelae were responsible for the death of 140 000 persons in the United States in 1924 The existence of a definite hereditary tendency has apparently been established Although elevation of the blood pressure may appear at any time it rarely occurs in children and is not commonly encountered in young adults It develops usually after the fourth decade of life over 80 per cent of Janeway's cases occurring after the fortieth and before the seventieth year The incidence figures for males and females indicate no striking difference although the frequent development of hypertension at the time of the menopause is noteworthy It occurs more frequently in individuals of the sthenic body type than in the asthenic The frequent association of hypertension with obesity is an observation of considerable practical importance It is thought to occur more frequently in tense overworked city dwellers than in the more phlegmatic leisurely rural population

The cause of essential hypertension is unknown Certain observations bearing upon the underlying nature of hypertension may be summarized

Experimental —Hypertension may be produced experimentally by (1) bilateral denervation of the carotid sinus and section of the aortic depressor nerve (Koch and Miles Heymans), (2) the production of a sudden increase in intracranial pressure and acute cerebral anemia by the injection of kaolin (Dixon and Heller) (3) subtotal nephrectomy (Cash Chanutin and Ferris), and (4) irradiation of the kidneys (Hartman Bolliger and Doub) Finally the work of Goldblatt Lynch Hanzal and Summerville reveals that renal ischemia in dogs induced by the application of clamps to the renal arteries results in a condition quite similar to that called essential hypertension in man Moderate impairment of the blood flow brings about an elevation of blood pressure with little or no gross disturbance of renal structure or function (*cf* benign hypertension) Severe constriction of the vessels leads to changes similar to those encountered in malignant hypertension in man The available evidence indicates that experimental hypertension resulting from renal ischemia is brought about by peripheral vasoconstriction and that this vasoconstriction is due probably to the presence in the blood of a pressor substance This pressor substance is thought by many investigators to be derived from the interaction of renin an enzyme like substance from the kidney and an activator in blood plasma The pressor substance has been called angiotonin (Page) and hypertensin (Munoz) It is further hypothecated that an antipressor substance exists in certain extracts of kidney intestinal mucosa and muscle tissue which is capable of inactivating the pressor substance This concept forms the basis for current attempts to treat hypertension by feeding or injecting renal extracts

Clinical —Hypertension may develop in man in association with acute and chronic glomerulonephritis bilateral or unilateral pyelonephritis prostatic obstruction or other types of obstruction to the flow of

urine, polycystic disease of the kidney tumors of the kidney renal amyloid disease periarteritis nodosa of renal arteries and renal artery occlusion, partial or complete due to embolism or arteriosclerotic narrowing Other conditions in which renal involvement is absent or not so conspicuous are endocrine disorders (Cushing syndrome ovarian and thyroid disease), polycythemia increased intracranial pressure, coarctation of the aorta

The above experimental and clinical observations have profoundly affected current concepts of essential hypertension and it is not surprising that the term renal hypertension is becoming popular again Is so called essential hypertension in truth renal hypertension? The practical importance of the question in those rare cases in which hypertension is not essential but actually due to unilateral renal disease has been demonstrated by the brilliant results which may follow appropriate therapeutic measures

Hypertension regardless of cause eventually produces changes in the heart and blood vessels The cardiac hypertrophy and arteriosclerosis which follow long standing essential hypertension differ in kind little if at all, from the cardiac and arterial lesions associated with chronic glomerulonephritis The earliest recognizable change produced in the heart is *hypertrophy of the left ventricle* This is due apparently to an increase in the thickness of the individual muscle fiber In association with this increase in the muscle mass (compensatory hypertrophy), there may be some deficiency in the supply of oxygen to the thickened muscle fibers (Harrison) Thus an inadequate supply of oxygen to the heart muscle may constitute a myocardial handicap in addition to the increased mechanical load of high blood pressure and contribute to the development of left ventricular dilatation



Fig 116—Essential hypertension Note hyaline thickening of the intima resulting in extreme narrowing of the lumen of a small renal artery (× 275 H & E Department of Pathology Vanderbilt University Hospital)

When the latter is sufficiently pronounced changes in the left auricle (hypertrophy dilatation) are conspicuous The right side of the heart is least affected in hypertension Nevertheless marked hypertrophy and dilatation of the chambers are often present in individuals with hypertension of long standing especially when failure of the left ventricle has occurred Heart failure attributable to either hypertrophy and dilatation from mechanical overloading or to coronary sclerosis and myocardial degeneration is the cause of death in approximately 60 per cent of patients with essential hypertension

As has been stated arteriosclerosis is

always present in long standing hypertension. Its occurrence in the coronary arteries has been referred to and is a common cause of coronary thrombosis and death. Cerebral arteriosclerosis secondary to hypertension frequently results in thrombosis or hemorrhage. Although changes may occur throughout practically the entire arterial system they develop first in the smaller vessels, the arterioles (arteriolosclerosis). Here the lesions are characterized by the presence of hyaline degeneration with or without fat, hyperplasia of the internal elastic membrane and proliferation of connective tissue in the intima and atrophy of the muscularis (Fishberg). In larger vessels hypertrophy of the muscular layers is usually conspicuous. The vessels of the viscera are involved in essential hypertension much more frequently than the vessels of the extremities. This is in striking contrast to senile arteriosclerosis which so often develops in the absence of hypertension.

In 72 cases of essential hypertension studied by Fishberg arteriolosclerosis was present in the kidneys in 100 per cent, spleen 66, pancreas 49, liver 30 and brain 19 per cent. However Fishberg and others have observed rare instances in which no renal arteriolar lesions whatsoever were demonstrated. Usually at autopsy well marked arteriolosclerosis with varying degrees of parenchymal atrophy are demonstrable. The cortex is thin, the arteries thickened and gaping. Arteriolosclerosis with secondary hyalinization of glomeruli, tubular atrophy and replacement fibrosis characterizes the kidney in essential hypertension of long duration. Death from uremia is relatively rare, occurring in less than 10 per cent of cases.

In the malignant type of essential hypertension the kidney presents a different picture from that described above. Its surface appears flea bitten as the result of numerous subcapsular hemorrhages. In addition to the arteriolosclerosis, glomerular hyalinization, tubular atrophy and fibrosis which are present in benign essential hypertension, a necrotizing endarteritis is present in the afferent and interlobular arterioles. The contiguous glomeruli may be necrotic and this is associated with marked degenerative changes in the corresponding tubules. The latter often contain blood and debris. The necrotizing endarteritis is not confined to the kidneys. As in benign hypertension the arteriolar lesions may be widely distributed. Changes in the optic nerve head and retina are of great diagnostic importance. Fishberg



Fig 117.—Malignant hypertension. Necrotizing sclerosis. Hyalinization and necrosis of the walls of an afferent arteriole (a) to glomerulus (d). The lumen of the arteriole is almost obliterated at (b) and completely obliterated at (c). (× 200 H & E Department of Pathology, Vanderbilt University Hospital.)

considers that they are consequences of hypertension and prefers the term "hypertensive neuro retinopathy" He considers that three factors may be involved con striction of the retinal arterioles lesions in the retinal arterioles and increased intra cranial pressure These produce circulatory disturbances in the retina of varying types depending upon which factor is dominant Edema of the nerve head and distended veins indicate increased intracranial pressure Thin columns of blood in the retinal arte rioles suggest constriction Hemorrhages and so called exudates (lipoid accumulations) are related to arteriolar lesions The major ity of patients with malignant hypertension die of uremia, commonly in association with congestive heart failure and not infre quently cerebral vascular accidents

Hugh J Morgan

BENIGN ESSENTIAL HYPERTENSION

Symptoms —In private practice the con dition is commonly discovered during the course of routine physical examinations, or examinations for life insurance on individ uals entirely free from symptoms Under such circumstances especially with neurotic patients it is important for the physician to avoid laying the foundation for an anxiety neurosis by attaching great significance to the observation It is sometimes a tempta tion to explain many symptoms on the basis of hypertension when the latter is present actually in an asymptomatic stage and such practice often results in failure to detect the real cause of the patient s complaints

Headache, vertigo restlessness insomnia asthenia, and loss of accustomed zest for living' are frequent early symptoms of hy pertension and may be encompassed by the unobservant patient in the sole complaint of a decline in general health In individuals past the fortieth year of life such complaints are common especially in the neurotic They should never be dismissed by the physician without careful consideration

Cardiac symptoms may constitute the in itial complaint Heart consciousness espe cially in the recumbent position palpitation inability to sleep without two or three pil lows instead of the accustomed one may exist for months or even years before impres sive evidence of diminished cardiac reserve or frank congestive heart failure ensues The latter is usually ushered in by dyspnea cough or cardiac asthma " symptoms due to failure of the left side of the heart As decompensation progresses the development of hepatic engorgement with tenderness edema of the dependent parts and transu dations into serous cavities indicate that fail ure of the right ventricle has ensued Symp toms of coronary artery disease may occur (angina pectoris, coronary thrombosis) with little or no relation to the manifestations of congestive heart failure, or they may be associated with this condition The majority of patients with essential hypertension even tually experience cardiac symptoms and die of heart failure

Symptoms indicative of cerebral arteriosclerosis occur frequently Approximately 20 per cent of deaths in essential hypertension are due to cerebral thrombosis or hemorrhage The sudden occurrence and rapid disappear ance of focal cerebral symptoms such as syn cope aphasia paresthesia monoplegia or hemiplegia or the development of more gen eralized cerebral manifestations as intense headache vomiting amaurosis drowsiness convulsions or coma without azotemia consti tute strong arguments for cerebral vascular spasm (Pal s Gefassenkrisen) the hyper tensive encephalopathy concept of Oppen heimer and Fishberg Hypertensive enceph alopathy is not a manifestation of renal insufficiency or uremia with which it may be easily confused especially when the gen eralized cerebral manifestations are present It is apparently caused by arterial hyperten sion regardless of whether the latter is due to acute or chronic glomerulonephritis essential hypertension eclampsia or other causes

Renal symptoms are not conspicuous Nocturia in association with diminished cardiac reserve is common It may when accompanied by polyuria indicate the pres ence of nephrosclerosis with impaired renal function in cases of long standing and it is almost always present in the malignant phase of essential hypertension

Physical Signs —The recognition of hypertension rests upon the results of the manometric determination of the blood pres

sure Certain physical signs usually accompany high blood pressure and may be listed as follows (1) the pulse may be hard and difficult to compress and thickening of the walls and elongation of the peripheral vessels may be present The brachial temporal and radial arteries may be conspicuously tortuous and pulsating (2) Ophthalmoscopic examination reveals varying degrees of arterial tortuosity Narrowing of the lumina of the vessels may be present The veins may appear nicked at points where they are crossed by arteries In more advanced cases with excessively high pressure and especially in malignant hypertension papilledema hemorrhage and retinal and choroidal lesions (exudate') occur (3) Increased retromanubrial dulness a diastolic shock over the aortic area and a ringing tympanitic aortic second sound a forceful localized thrust at the apex of the heart enlargement of the heart downward and to the left—these in varying degrees are commonly present

The urine may be entirely normal Traces of albumin hyaline and finely granular casts and occasional red blood cells may be present Renal function as determined by urine concentration tests phenolsulfonphthalein excretion blood nitrogen determination and the urea clearance test is usually normal

The electrocardiogram as a rule exhibits left axis deviation together with inversion of the T wave in lead I

The blood pressure readings vary greatly not only in different patients but often in the same patient When the systolic pressure is consistently more than 140 mm of mercury it is definitely abnormal The term hypertension is reserved by many to indicate systolic pressures of 160 mm or more and in essential hypertension there is a commensurate rise to 90 mm or more in the diastolic pressure The blood pressure may be observed to rise rapidly from month to month more slowly from year to year or to remain stationary It is not unusual to observe variations in pressure of from 30 to 40 mm during an office visit

Prognosis —The height of the systolic and diastolic blood pressure is an extremely important factor in prognosis Frost s tables indicate that mortality increases in direct proportion to the elevation above the normal of the systolic pressure However marked variations occur Allbutt observed a patient for eighteen years after the discovery that the blood pressure was 250 mm ! The height of the diastolic pressure is of especial prognostic significance since a diastolic pressure in excess of 150 mm usually indicates that the hypertension has entered the malignant phase and this is followed soon in most instances by uremia congestive heart failure or less frequently cerebral vascular accident In normal individuals the blood pressure levels usually rise with increasing weight In essential hypertension obesity can be shown frequently to be responsible for an appreciable increment of the pressure More important from the standpoint of prognosis perhaps is the extra work performed by the heart in the obese an excess above that entailed by hypertension alone Paullin and others have noted that women with hypertension survive much longer than men This is possibly a reflection of the usually benign character of the hypertension which may develop in association with the menopause Age is an important factor the younger the patient the more unfavorable the outlook Hemorrhages associated with white spots in the retina (hypertensive neuro retinopathy) are ominous signs Death commonly follows within a year Hypertension leads to death from heart disease in approximately 60 per cent of cases from cerebral hemorrhage or thrombosis in 20 per cent and uremia in 10 per cent

Diagnosis —The very definition of essential hypertension renders it necessary that inflammatory kidney disease and urinary tract obstruction be excluded before the term can be properly applied in diagnosis This has been discussed under etiology and pathogenesis Interest in hypertension has been greatly stimulated by recent experimental work and this is reflected in a more critical use of the term essential hypertension in diagnosis Thus cases which formerly would have been classified essential hypertension are now being recognized as exhibiting hypertension directly related to endocrine disorders (pituitary basophilism tumors or hyperplasia of the adrenal cortex menopause) obstruction to the flow of urine (congenital anomalies ureteral and urethral obstructions and so on) urinary tract in

fections (pyelitis pyelonephritis) renal artery disease (narrowing of lumen by arteriosclerosis, infarcts) tumors of the kidney coarctation of the aorta, and others Heretofore interest centered chiefly in the separation of certain cases of hypertension from acute and chronic glomerulonephritis These were labeled essential hypertension When the clinician excluded glomerulonephritis the diagnosis of essential hypertension almost became automatic and etiologic interest promptly dwindled Of course nephritis still remains the commonest problem in differential diagnosis Nevertheless recent work in experimental hypertension has redirected attention to the kidney and has stimulated more critical study of patients with hypertension especially with reference to the possible existence of primary remedial urinary tract disease A considerable number of cases have been reported in which striking improvement or disappearance of hypertension has followed the removal of the diseased kidney in unilateral hydronephrosis pyelonephritis and tumor or the relief of urinary obstruction due to prostate or stricture or the treatment of renal pelvis infection

It should be borne in mind that very infrequently, hypertension which develops at the time of the menopause may be transient Hypertension occurring before the age of forty years suggests nephritis After forty essential hypertension is a common disorder and glomerulonephritis is relatively uncommon Extremely high arterial pressures are more apt to be associated with essential hypertension especially malignant essential hypertension than with glomerulonephritis A past history of acute glomerulonephritis is strong circumstantial evidence that subsequent hypertension is due to chronic glomerulonephritis The malignant phase of essential hypertension may present a picture similar in all respects to chronic glomerulonephritis

Treatment —Many patients with benign essential hypertension require no treatment When treatment is indicated it is directed toward protecting the patient as far as this is possible, from the consequences of the disorder rather than toward lowering the blood pressure The latter may be accomplished in the obese by weight reduction in the apprehensive, nervous overworked individual by reassurance and measures conducive to rest and relaxation However the reduction in pressure which follows correction of these secondary factors is usually temporary The patient should develop 'a way of life' compatible with the handicap which exists Careful consideration should be given by the physician to the personal problem involved Sedatives (phenobarbital 0 03 Gm three times a day, bromide 1 Gm twice daily) are useful especially to reduce nervous tension and allay apprehension Estrogenic preparations may be useful in climacteric hypertension' Drugs which are prescribed specifically for blood pressure reduction are of little value This statement applies to the continuous administration of potassium thiocyanate the nitrates extracts of mistletoe garlic or watermelon seed veratrum viride acetylcholine and nicotinic acid Except for the temporary effects obtainable from hypnotics narcotics anesthetics and vasodilators during critical elevation or crises of hypertension which are due to psychic disturbances or pain little can be accomplished with drugs Critically evaluated clinical and experimental evidence indicates that the results of treatment by renal extracts are irregular and possibly nonspecific The nitrites are sometimes employed for headache A combination of acetylsalicylic acid 0 3 Gm phenacetine 0.3 Gm and caffeine citrate 0 15 Gm is more effective Physiotherapy (relaxing hydrotherapy and massage) is very useful Diet plays an unimportant role though excessive sweets overeating and condiments are to be avoided Physical activity is ordered in such a way as to avoid periods of sudden physical strain thus conserving cardiac reserve

The *surgical treatment* of essential hypertension by renal denervation splanchnic denervation or partial adrenalectomy is in the experimental stage The outlook is not very encouraging

The *management* of hypertensive heart disease is discussed elsewhere When urgent cardiac symptoms are present as a result of acute left ventricular failure and pulmonary edema prompt venesection morphine and oxygen may save life *If the diastolic* blood pressure is over 100 digitalis in small daily doses (Christian) appears to be

rational treatment and when employed with appropriate regulation of physical activity it doubtless postpones the advent of congestive heart failure The treatment of cerebral thrombosis and hemorrhage and of nephrosclerosis and renal insufficiency is discussed elsewhere

In the treatment of hypertensive encephalopathy whether associated with essential hypertension acute or chronic glomerulonephritis or eclampsia the following measures are important (1) a reduction of the intracranial pressure if lumbar puncture reveals it to be increased by cautious slow drainage of cerebrospinal fluid and the use intravenously of hypertonic sugar solutions (2) venesection (in adults who are not anemic 500 cc is the amount of blood usually removed) and (3) morphine magnesium sulfate and the barbiturates as antispasmodics and sedatives

HUGH J MORGAN

MALIGNANT ESSENTIAL HYPERTENSION

In hospital practice one encounters not infrequently individuals with essential hypertension in whom the entire clinical course from the appearance of symptoms until death is telescoped into a period of months or a year or two In others after years of relatively asymptomatic or benign hypertension a marked intensification of symptoms and acceleration of progression occurs Negroes appear to be particularly susceptible Necrotizing endarteritis of the renal arterioles with extensive glomerular and tubular changes constitutes the characteristic renal lesions The pathologic changes can be reproduced experimentally by severe constriction of the renal arteries (Goldblatt) Fishberg describes the clinical picture as one characterized by manifestations of increased intracranial pressure (headache vomiting papilledema) and renal insufficiency (albuminuria cylindruria hematuria nitrogen and phenolsulfonphthalein retention) Stupor and frequently convulsions occur Commonly the evidence of renal insufficiency afforded by the laboratory is quantitatively not as great as might be expected were the uremic state due to chronic nephritis The systolic blood pressure is usually excessively high 220 to 250 mm and more and the diastolic pressure is correspondingly elevated Retinal hemorrhages and white spots together with papilledema characterize the ophthalmoscopic findings Manifest congestive heart failure commonly complicates the clinical picture and cerebral vascular accidents are not infrequent The condition is invariably fatal

HUGH J MORGAN

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HYPOTENSION

Under normal conditions the blood pressure in the aorta is about 10 mm higher than in the brachial arteries in the digital arteries it is about 10 mm lower than in the brachial This represents a drop of approximately 20 mm from the aorta to the periphery Beyond the arterioles the pressure falls markedly for the normal capillary blood pressure is usually stated to be between 25 and 10 mm of mercury The regu

latory mechanism of the arterioles, then chiefly determines the pressure of the blood in the capillaries maintaining it at a more or less constant level regardless of the arterial pressure Thus the efficiency of the capillary circulation need not suffer in the least from moderate alterations of the arterial blood pressure This doubtless is the explanation of the fact that individuals with relatively low blood pressures may experience *no untoward effects*

There is no agreement as to the etiology or clinical significance of the constantly low blood pressure levels which are present in some patients The average blood pressure of normal Orientals is distinctly lower than that of Europeans and Americans It is impossible to arrive at a figure for the minimal normal level of the blood pressure in health Certainly one observes patients commonly enough whose circulatory efficiency is in no sense impaired by systolic pressure of 110 mm or lower ('essential hypotension') Indeed in the mass low blood pressure favors longevity distinctly Nevertheless psychoneurotic states including neurocirculatory asthenia have been ascribed to hypotension constitutional factors splanchnoptosis and capillary stasis have been implicated in etiologic considerations of the latter In the psychoneuroses hypotension is more often an effect than it is a cause Low blood pressure is frequently found in association with wasting diseases (malignancy chronic infection) anemia malnutrition hypothyroidism myocardial insufficiency amyloid disease and others

It is important to recognize the significance of hypotension in certain clearly defined reflex and organic disorders It is an important clinical manifestation of Addison s disease in which the blood pressure remains usually at a persistently low level Common *fainting attacks* are associated with a progressive decrease in pulse pressure and a decreased venous return to the heart In individuals with *hypersensitive carotid sinuses* pressure on the sinus at the bifurcation of the common carotid artery may be associated with the development of bradycardia hypotension and syncope and rarely convulsive twitchings This may be due to an abnormally sensitive carotid sinus without demonstrable lesions or to hypersensitiveness of the carotid sinus reflex due to arteriosclerosis or to tumors at or near the bifurcation of the carotid artery The disturbance may be either unilateral or bilateral Spontaneous attacks occur without apparent cause in periods of emotional excitement or with sudden changes in the position of the head Weiss cites the case of a street car motorman who wore a stiff collar which induced attacks when the head was suddenly turned Digitalis renders the carotid sinus reflex hyperactive and may thus be a factor in precipitating attacks especially when arteriosclerosis is present Diagnosis rests upon the reproduction of the spontaneous attacks by pressure on one or both carotid sinuses Atropine and ephedrine have been found useful in treatment When involvement is unilateral surgical treatment consisting of carotid denervation has proved successful This should not be attempted unless the reflex can be abolished temporarily by novocainization of the sinus region

Postural or *orthostatic hypotension* is brought about by a sudden change from the horizontal to the upright position or by prolonged standing and is due to failure of the blood pressure regulatory mechanisms to adjust themselves to changes of posture For example a systolic pressure of 140 mm of mercury, when the patient is supine may fall to 115 mm when a sitting position is assumed and to 70 mm or lower when the patient stands The diastolic pressure exhibits corresponding reductions Normally with these changes in posture the systolic blood pressure drops only slightly and the diastolic pressure tends to rise When orthostatic hypotension is present both systolic and diastolic pressures fall and weakness faintness syncope and even convulsive seizures may occur Hypersensitiveness of the carotid sinus reflex may be demonstrable Ephedrine sulfate (0 025 to 0 05 Gm) or Benzedrine sulfate (0 005 to 0 01 Gm) administered several times a day and abdominal supports have been employed successfully

Hyperinsulinism internal hemorrhages vascular occlusions and shock from any cause are commonly associated with a rapid fall in the blood pressure

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DISEASES OF THE HEART

DISEASES OF THE PERICARDIUM

ACUTE FIBRINOUS PERICARDITIS

Definition—Acute fibrinous pericarditis is an inflammation of the pericardium associated with the formation of a fibrinous exudate on the serous membrane The lesion may not pass beyond this stage but in some cases it does and a serous serosanguineous or purulent exudate may form (*pericarditis with effusion*)

Etiology—Pericarditis is probably never a primary disease The six most frequent pathologic conditions with which it is associated are (1) rheumatic fever (2) pneumococcal infections especially empyema (3) pulmonary tuberculosis (4) chronic nephritis with uremia (5) coronary thrombosis with myocardial infarction (6) perforating wounds of the thorax Not uncommonly acute pericarditis may be caused by an infection of unknown etiology as in polyserositis (*Concato s disease*) The micro-organisms most frequently found in the pericardial exudate are the pneumococcus the tubercle bacillus and the pyogenic organisms especially the streptococcus The gonococcus the colon bacillus and the influenza bacillus have occasionally been cultivated from the pericardial exudate In scarlet fever meningococcus meningitis pertussis parotitis and measles acute pericarditis is a rare complication Actinomycosis and malignant tumors may cause pericarditis Recently pericarditis has been observed in tularemia and undulant fever

Morbid Anatomy—Acute pericarditis is associated with an outpouring of fibrin This may be exuded on the pericardial surfaces without effusion of fluid (*dry pericarditis*) or serum may be admixed with the fibrin (*serofibrinous pericarditis*)

Symptoms—Since pericarditis is secondary to disease elsewhere in the body the symptomatology is influenced by the character of the primary or underlying disorder Acute fibrinous pericarditis *per se* is usually painless Where pain occurs one of two complications is likely to be present first a large pericardial effusion which may cause dull aching pain in the precordium second pleuropericarditis especially if the diaphragmatic pleura is affected The pain may be localized in the chest or referred to the neck or abdomen

The pericarditis of nephritis and other terminal conditions is painless probably because complicating pleuropericarditis is infrequent

Physical Examination—Palpation occasionally reveals a friction fremitus caused by the rubbing together of the roughened pericardial surface *Auscultation* yields the most important and not infrequently the sole evidence of fibrinous pericarditis The friction rub is a to and fro sound close to the ear which corresponds to systole and diastole and varies greatly in intensity in different cases and often in the same case The timing of the sound differs from the timing of a to and fro valvular murmur in that it does not begin immediately after the heart sounds and generally overlaps them The rub may be only a slight scratchy noise perceptible with some difficulty and easily overlooked or an intense grating sound In rare instances it may be audible without a stethoscope a few inches from the chest wall It may be heard at one examination and be absent at the next not infrequently it persists only a few hours but it may recur with increased intensity It disappears if a fluid exudate *completely separates* the layers of the pericardium However a pericardial friction rub frequently is audible in the presence of large effusions The rub is most frequently heard over the right ventricle in the fourth and fifth spaces close to the sternum it is however often encountered at the base of the heart or at the apex In rare instances it may be heard posteriorly in the left thorax At times the intensity of the friction is augmented by pressure with the stethoscope Unlike endocardial murmurs peri

cardial friction is not transmitted in definite directions Change of position of the patient may alter the rub s intensity considerably

Diagnosis—The friction rub is pathognomonic of the disease but since it is often present for only a few hours repeated examination of the heart is necessary Difficulty in diagnosis arises if there is intense pain without friction rub at the onset A scratchy or crepitant quality of the heart sounds, particularly the first sound in the tricuspid and pulmonary areas is encountered in a small percentage of normal hearts and may be differentiated from a friction rub by its constancy by its more definite timing with the heart sounds by the fact that it does not change under pressure with the stethoscope and by the absence of fever or other symptoms

A *pleuropericardial friction rub* must be differentiated from a pure pericardial rub The former has in addition to the to and fro rhythm definite intensifications associated with the respiratory cycle which may be temporarily abolished by cessation of breathing The bubbling crunching sounds heard in mediastinal emphysema may be differentiated from a pericardial friction rub by their peculiar acoustics Also the patient with spontaneous interstitial emphysema while he may have severe pain usually presents no clinical signs of infection or of cardiac disease

Electrocardiographic changes in acute pericarditis occur in approximately 65 per cent of all cases and in some instances can be differentiated from electrocardiograms of coronary heart disease by serial tracings The RS T segments may be elevated in all the standard leads in the combined leads I and II or only in lead I The reciprocal depression of the RS T segment in lead III usually seen in anterior infarction due to coronary occlusion does not occur in pericarditis

A second helpful point in differentiation between coronary occlusion and pericarditis is the fact that in the early stages of pericarditis the RS T segment is *concave* upward or straight while in myocardial infarction it is *convex* upward

In acute pericarditis the T waves are upright in the early stages of the disease and may be of increased amplitude Later they may remain upright or become inverted in all of the leads an electrocardiographic finding not often encountered in any other variety of heart disease Occasionally inversion of the T wave in lead I develops while the upright T wave in lead III persists thus simulating the electrocardiographic pattern following infarction of the anterior apical region of the heart

In the apical precordial lead S T segment elevations may occur and the T wave may become inverted However a prominent Q_4 does not appear and the R wave is usually normal in amplitude

Prognosis—The prognosis in acute fibrinous pericarditis is good, provided the underlying disease is not fatal Adhesions of the layers of the pericardium by organized fibrinous exudate are a common sequel and the patient should be followed carefully for the possible development of pericardial effusion or chronic constrictive pericarditis

Treatment—Rest in bed is the essential element of treatment Application to the precordium of an ice bag often affords relief When the pain is severe codeine or morphine is required As the disease is usually secondary to infection elsewhere in the body treatment of the primary disease is obviously most important Sulfonamide derivatives should be administered if pyopericardium develops (see below Pericarditis with Effusion)

JOHNSON MCGUIRE

PERICARDITIS WITH EFFUSION

Definition—Pericarditis with effusion is associated with inflammation of the pericardium during the course of which a fluid exudate collects in the pericardial cavity

Etiology—Pericardial effusion may follow pericarditis due to any of the causative factors described under Acute Fibrinous Pericarditis Pyogenic infections tuberculosis and rheumatic fever are the commonest etiologic agents responsible for pericardial effusion

Morbid Anatomy—The visceral and parietal layers of the pericardium may be covered with varying quantities of fibrin so abundant as to form a coarse shaggy coat

which at times greatly interferes with aspiration of fluid from the sac The fluid exudate may be of several kinds—serous serosanguineous hemorrhagic seropurulent or purulent—but whatever its nature flakes of fibrin are generally found floating in it The quantity of fluid contained in the pericardial cavity varies greatly, in some cases only 100 to 200 cc may be found while in others 1.5 or 2 liters may distend the sac In contrast to transudates the inflammatory exudates have a relatively high specific gravity (1 017 +) and usually a total protein content of more than 30 Gm per liter The fluid is clear serous or cloudy, according to the number of cells and amount of fibrin contained In purulent exudates a thick creamy pus may be found which at times has a putrid odor In the fluids generally associated with tuberculosis neoplasm purpura rheumatic fever or streptococcal infections red corpuscles are more or less abundant while in the purulent exudates pus cells are so numerous as to dominate the field many of the cells are necrotic and stain imperfectly

Pathologic Physiology—Pericardial effusion of sufficient magnitude to produce clinical manifestations does so primarily by causing cardiac tamponade as follows (1) Blood enters the heart with difficulty since the pressure of the fluid between the distended *pericardium and the heart impedes* the entrance of blood from the great veins into the heart This causes a rise of peripheral venous pressure from the normal 5 to 10 cm of water to levels of from 15 to 40 cm of water (2) The cardiac output per minute and per beat is decreased from the normal of ± 3 87 liters per minute to about 2 liters per minute and the stroke volume from the normal of 64 cc to less than 40 cc (3) The lowered cardiac output produces a decrease in arterial blood pressure to approximately 110 90 mm of mercury with a small pulse pressure of about 20 mm of mercury (4) The pulse rate is increased probably due to a compensatory reflex to aid the total blood flow per minute since the output per beat is decreased (5) The velocity of blood flow is diminished as measured from arm to the tongue (6) The movements of the heart are decreased as seen fluoroscopically or in the roentgenkymograph (7) During inspiration the pulse becomes weak or imperceptible This valuable sign of cardiac tamponade while not pathognomonic of this condition is called the pulsus paradoxus and is thought by Katz and Gauchat to be due to the decrease of the normal differential pressure during inspiration between the intrathoracic intrapericardial and extrapericardial veins

The effects of acute cardiac tamponade are described below under Pericardial Diseases as a cause of acute cardiac tamponade

Symptoms—The onset of pericarditis with effusion is seldom abrupt and often very insidious Because the disease is frequently secondary to serious trouble elsewhere in the body it may not perceptibly alter the general condition of the patient The fever is usually of the same type as that of the primary disease although it may be somewhat aggravated

The disease often causes little or no local discomfort If *pain* develops it may be localized or referred as in acute fibrinous pericarditis The intensity of the pain varies there may be merely a dull heavy feeling of discomfort or the most severe stabbing cutting or constricting pain

Dyspnea is usually though not invariably present and orthopnea is common with large effusions Generally the *alae nasi* dilate on *inspiration*

A marked distention of the pericardial cavity may *irritate nearby nerves* Irritation of the recurrent laryngeal nerve may lead to laryngeal paralysis and aphonia irritation of the vagus or pressure on the esophagus to difficulty in swallowing pressure on the phrenic nerves to hiccup An aggravating cough which is usually without expectoration may result from pressure on the trachea and bronchi

Physical Examination—*Inspection* may show a fulness or bulging of the precordium especially in children The apex impulse is often not visible particularly if the effusion is large Fulness of the interspaces may be noted and at times edema of the chest wall particularly in pyopericardium Expansion of the left side of the chest is lessened by large effusions Bulging in the epigastrium may be due to depression of the left lobe of the liver The superficial veins of the neck

thorax and upper *extremities are usually* distended

Palpation—Friction fremitus generally disappears as fluid accumulates but it may be continuously found at the base of the heart with the patient erect even in cases with considerable effusion As the quantity of fluid increases the apex impulse usually becomes less and less distinct until finally, it is no longer palpable, unless the heart is fixed to the anterior chest wall by localized adhesions A vanishing apex impulse is one of the important signs of collection of fluid *in the pericardium particularly when accom* panied by an increase in the relative cardiac dulness

Percussion—The *most valuable single sign of pericardial effusion* is dulness at the base of the heart in the first and second interspaces shifting with change in posture of the patient It is most satisfactorily dem onstrated by Hoover s method of direct per cussion with the middle finger

Widening *of the area of relative dulness* in the first and second interspaces to the right and left of the sternum may be the first evidence of effusion and may precede widening of the right and left borders of cardiac dulness The area of dulness in the first and second interspaces should be mapped out with the patient first recum bent then erect A narrowing of the area of dulness in the erect posture indicates ef fusion *in the pericardial sac*

Likewise the areas of relative cardiac dul ness to the right and left of the inferior cardiac borders also shift with change of position in the presence of effusion but the change here is just the reverse of the change at the base of the heart Thus when the patient sits up the relative dulness ex tends further to the right in the fourth inter space and further to the left in the fourth and *fifth interspaces*

In case of large effusions there may be impairment of the percussion note at the angle of the *left scapula*

Auscultation—A friction rub present at the onset may disappear as accumulating fluid separates the visceral from the parietal pericardium However *if adhesions are pres* ent the friction rub may persist despite the presence of a large effusion With large ef fusions the heart sounds are usually distant *and feeble* At the angle of the left scapula bronchial breathing and pectoriloquy may be present due to compression of the lung by the distended *pericardium* *This physical* finding is called Ewart s sign and is thought by Levine to occur only in rheumatic peri carditis and to be due not to pulmonary compression but to rheumatic pneumonia However this has not been our experience

Radiography—Roesler s studies have con tributed much to the roentgenographic find ings in pericarditis When 300 cc of fluid accumulate in the pericardium definite *x ray changes—the earliest evidence of ef* fusion—appear Even with effusion of mod erate size a bulging of the lowest margin of the cardiac silhouette can be demonstrated In the lateral view there is a convexity pos teriorly where normally the straight contour of the vena cava is seen As additional fluid accumulates the pulsations of the heart as seen fluoroscopically become decreased in amplitude and may cease entirely However *with severe myocardial disease the cardiac* pulsations may likewise become impercep tible Finally with a large effusion the heart assumes a pear shape or water bottle ap pearance The normal curves of the heart can no longer be seen and the transverse diameter may exceed the longitudinal *It is* not always possible by any roentgenographic method to differentiate between dilatation and effusion Roentgen kymography serves *as an excellent check* upon fluoroscopic ex amination when there is doubt concerning the magnitude and character of the cardiac pulsations

Differential Diagnosis—Differentiation must be made between pericardial effusion and cardiac hypertrophy and dilatation In *chronic hypertrophy and dilatation of the heart* the shadow is not so typically pear shaped and does not extend so high along the sternal margins nor so low in the fifth and sixth interspaces on the right Moreover the cardiac measurements in the sitting and in the recumbent position do not undergo the changes so characteristic *of pericardial* ef fusion Fluoroscopic examination usually re veals a well marked forceful pulsation Dila tation of the heart presents great *diagnostic* difficulties Osler has summarized the *most* important differences in the following words (1) The character of the apical impulse in

dilatation particularly in thin-chested people is commonly visible and wavy (2) The shock of the cardiac sound is more distinctly palpable in dilatation (3) The area of dulness in dilatation rarely has a triangular form nor does it except in cases of mitral stenosis reach so high along the left sternal margin or so low in the fifth and sixth interspaces without visible or palpable impulse Dulness shifting with change of position speaks strongly for effusion (4) In dilatation the heart sounds are clearer often sharp or fetal in character gallop rhythm is common whereas in effusion the sounds are distant and muffled (5) Rarely in dilatation is the distention sufficient to compress the lung and produce the tympanitic note in the axillary region or flatness behind (6) The x ray picture may be very definite and unlike any form of dilatation or hypertrophy of the heart

In children of less than one year the shadow of an *enlarged thymus gland* merging with that of the heart may closely resemble the shadow characteristic of pericarditis with a moderate amount of effusion An enlarged thymus however does not change shape with change of position

Diagnosis —The diagnosis of pericardial effusion is often difficult especially if the effusion is not fully developed when the first examination is made If however the patient is examined from day to day as the fluid collects the physical signs usually do permit recognition of the condition in the course of time In doubtful cases fluoroscopic examination may aid greatly in diagnosis

Early in the course of an effusion when the exudate collects rapidly the increased intrapericardial pressure may narrow the coronary vessels sufficiently to produce changes in the electrocardiograms resembling those seen in cases of coronary occlusion (see *Electrocardiographic* changes under Acute Fibrinous Pericarditis) As the symptoms at times also closely resemble those of a coronary thrombosis differential diagnosis may be extremely difficult Sooner or later however signs of pericardial effusion become definite With a large effusion there is often low voltage of all complexes

Diagnostic puncture is the means by which the existence of a pericardial effusion may be definitely demonstrated However it must be remembered that attempts at pericardial aspiration may lead to fatal accidents if the ventricular walls are lacerated or if the coronary vessels torn Indications for pericardial aspiration are two (1) Therapeutic aspiration for the relief of cardiac tamponade when clinical and laboratory data including markedly elevated or steadily rising venous pressure and markedly low or progressively falling arterial pressure indicate the necessity of relieving increased intrapericardial pressure (2) Diagnostic aspiration to determine if purulent pericarditis is present a condition requiring surgical drainage The majority of clinicians believe that the best site for aspiration in pericardial effusion is the fifth left interspace at the outer border of percussion dulness which is of course outside the apical impulse The needle preferably should be attached to a syringe by a three-way stop cock and inserted inward upward and backward If fluid is not encountered promptly or if the cardiac contractions are felt with the needle it is wise to discontinue the procedure at once as either little fluid is present or it is situated elsewhere

In the occasional case where x ray examination shows the fluid to be principally located to the right of the sternum aspiration should be carried out in the fourth right interspace taking care to avoid the internal mammary artery

Occasionally aspiration is successful posteriorly at the angle of the left scapula (if Ewart s sign is present) even though the anterior approach has been unsatisfactory In France there is considerable enthusiasm for the epigastric approach With this technic the needle is inserted just below the lower border of the ensiform cartilage The bevel of the needle should be kept close to the undersurface of the sternum while it is being pushed upward to enter the pericardial cavity above the diaphragm

Prognosis —The duration of the disease depends to a considerable extent upon the nature of the exudate and upon the underlying exciting cause In pericarditis of pyogenic etiology the mortality is high Whitehill and Harvey have reported a mortality of 85 per cent in tuberculous pericarditis whereas in rheumatic cases the prognosis

depends upon the condition of the myocardium

Treatment—Pericardial paracentesis and the aspiration of the pericardial fluid are indicated when the quantity of exudate is sufficient to produce symptoms of cardiac tamponade In rheumatic pericarditis spontaneous absorption often occurs and a conservative attitude is indicated unless the symptoms of tamponade are pronounced In *tuberculous pericarditis frequent aspirations* may be required If thick pus is present rib resection and surgical drainage are necessary Use of sulfonamide derivatives should be employed in pyopericardium in conjunction with surgical drainage if the etiologic agent is susceptible to these drugs In the average case an initial dose of 4 Gm (60 grains) of the sulfonamide chosen followed by 1 Gm (15 grains) every four hours will secure the desired level of the drug in the blood and pericardial fluid

JOHNSON MCGUIRE

ADHESIVE PERICARDITIS

(Adherent Pericardium Chronic Constrictive Pericarditis Pick s Disease Pericardial Scar Concretio Cordis Accretio Cordis)

Definition—Adherent pericardium is a condition resulting from fibrous adhesions between epicardium and pericardium or between the parietal pericardium and various intrathoracic structures Obliteration of the pericardial cavity may be partial or it may be completely obliterated by dense scar tissue (*concretio cordis*) There may also be adhesions extending from the pericardium to the mediastinum the pleurae the diaphragm and the chest wall (*accretio cordis*)

Etiology—Adherent pericardium is usually the result of a previous acute pericarditis and a history of antecedent pericarditis can often be obtained Tuberculosis and pneumococcal infections are frequently responsible Most commonly adhesive pericardial fibrosis is caused by an infection of unknown etiology Rheumatic fever frequently causes pericarditis however rheumatic pericarditis never causes the thick callous pericardial scar of chronic constrictive pericarditis A case of chronic constrictive pericarditis following and probably caused by tularemia has recently been successfully treated surgically at the Cincinnati General Hospital

Pathology and Pathologic Physiology—White has classified adherent pericardium under several groups *First* loose strands of fibrous tissue may join the epicardium to the pericardium Such adhesions have no effect on the function or size of the heart *Second* the visceral and parietal pericardium may be completely adherent but the heart is not bound to the intrathoracic structures by adhesions In such cases the pericardium is not greatly thickened the heart is not seriously handicapped and no cardiac enlargement results *Third* there may be great thickening of the pericardium with the heart encased and constricted by a dense envelope of fibrous tissue Calcium or bone may be found embedded in this scar tissue This condition has been termed *chronic constrictive pericarditis (concretio cordis)* Chronic constrictive pericarditis causes chronic cardiac compression the inflow of blood in diastole is impeded venous pressure is increased and enlargement of the liver and ascites follow The cardiac output is markedly diminished and the circulation time prolonged often to the same degree as in congestive heart failure Because of the inelastic scar tissue surrounding the heart hypertrophy cannot occur even when external adhesions develop and require extra work during systole *Fourth* adhesive pericarditis uniting the visceral and parietal pericardium may be associated with external adhesions binding the heart to the pleurae the diaphragm the costal cartilages or the sternum (*mediastinopericarditis* or *accretio cordis*) In this type of adherent pericardium an extreme degree of cardiac hypertrophy has been described and has been attributed to an increase in work during systole as the heart tugs against the fixed adhesions In recent years there has been considerable controversy regarding the influence of adherent pericardium as a factor in causing cardiac enlargement From a review of sixty five cases of adherent pericardium proved by autopsy at the Cincinnati General Hospital it is our opinion that a moderate degree of cardiac enlargement may follow the addi

tional work necessitated by the pull of the heart against the adhesions during systole However in our series and apparently in Cabot s as well the hearts of extraordinary size (sometimes weighing more than 1000 Gm) not only had internal as well as external pericardial adhesions but also some complicating handicap such as hypertension or valvular disease

The enlargement of the liver in certain cases of adherent pericardium was first described by Pick in 1896 This enlargement of the liver he designated pseudocirrhosis of the liver' The condition is caused by long standing chronic passive congestion of the liver brought about from obstruction of venous return by encasing pericarditis Firmness of the liver according to modern concepts results from a relative increase in connective tissue following necrosis of parenchymatous cells

Symptoms and Signs—Clinically adherent pericardium may be divided into three groups

1 *Asymptomatic Group*—In the majority of cases adhesions between the visceral and parietal pericardium or adhesions between the parietal pericardium and intrathoracic structures cause no symptoms or signs Thus the disorder may first be discovered at autopsy death occurring from some unrelated cause

2 *Chronic Constrictive Pericarditis* (*Concretio Cordis*) —SYMPTOMS —Enlargement of the abdomen and prominence of the veins of the neck and often edema of the feet and legs are the commonest symptoms Dyspnea weakness malnutrition are inconstantly present

PHYSICAL SIGNS —Inspection reveals conspicuous engorgement of the veins of the neck (the venous pressure may be 20–45 cm of water *i e* two to five times the normal) The distention of the veins is often present in the sitting as well as in the recumbent position Cyanosis of the lips and nail beds may be present Inspiratory swelling of the veins of the neck is a common and important sign Orthopnea is inconstant There is moderate or even extreme enlargement of the abdomen usually with a fluid wave Pitting edema of the legs and ankles is often found The liver is regularly enlarged and firm but usually it is not tender and does not pulsate Splenomegaly rarely occurs The pulse is small the systolic blood pressure and pulse pressure are characteristically low or within the lower limits of normal A paradoxical pulse (a fall in systolic blood pressure during inspiration) may be observed Pleural effusion is commonly present The fluid like that found in the abdomen usually has the characteristics of a transudate

The heart is usually small and quiet In most cases the rhythm is regular but irregularity arising from auricular fibrillation or extrasystoles is sometimes encountered The sounds may be distant but otherwise are of normal intensity Systolic apical murmurs may be present

The ELECTROCARDIOGRAM is helpful in the recognition of chronic constrictive pericarditis Usually there is low voltage of QRS complexes and the T waves are frequently of low amplitude or negative If the heart be immobilized by adhesions the electric axis may not alter with change of position of the body but fixation of the electric axis is by no means pathognomonic The detection by x ray of calcareous deposits encircling the heart is helpful in confirming the diagnosis of adherent pericardium The cardiac silhouette is usually of normal size though marked thickening of the pericardium may suggest hypertrophy or dilatation Decrease in the amplitude of the pulsations of the heart particularly of the right border is the usual *fluoroscopic* finding

DIFFERENTIAL DIAGNOSIS —Chronic constrictive pericarditis must be differentiated from the following disorders

ARTERIOSCLEROTIC HEART DISEASE WITH CONGESTIVE HEART FAILURE —High venous pressure ascites and a feebly pulsating heart are not uncommon in congestive heart disease due to coronary artery sclerosis as well as stenosis of coronary ostia due to syphilis The history the electrocardiogram the persistence of an elevated venous pressure despite bed rest and digitalization in constrictive pericarditis help to differentiate the two conditions Also careful x ray and fluoroscopic studies may demonstrate evidence of calcium deposits within the pericardium itself

MITRAL AND TRICUSPID VALVULAR DISEASE —Enlargement of the liver edema and

dilatation of the cervical veins are commonly present with tricuspid stenosis and failure of the right heart secondary to mitral stenosis The history, configuration of the heart and the presence of a presystolic or diastolic murmur are helpful differential findings

BERIBERI HEART —The generalized edema and signs of right sided heart failure in this condition are theoretically confusing The history of dietary deficiency peripheral neuritis tenderness and atrophy of the muscles therapeutic response to vitamin B_1 in beri beri and the enlarged liver fluoroscopic and electrocardiographic findings in chronic constrictive pericarditis help to differentiate these diseases

PORTAL CIRRHOSIS OF THE LIVER—The age of the patient with cirrhosis of the liver the history of alcoholism the absence of venous engorgement of the cervical veins the presence of splenomegaly and the absence of signs referable to the heart make the differentiation from adherent pericardium comparatively simple In fact the normal level of venous pressure in the veins of the arm in hepatic cirrhosis eliminates Pick s disease from consideration

POLYSEROSITIS —In polyserositis the serous effusions are primarily inflammatory In adherent pericardium effusion into the pleural and pericardial cavities results from elevated venous pressure and chronic passive congestion

3 *External Pericardial Adhesions* (*Mediastinopericarditis Accretio Cordis*) —SYMPTOMS —Unless the symptoms of myocardial insufficiency are present there are no characteristic symptoms of external pericardial adhesions

SIGNS —The most important physical sign of external adhesions is systolic retraction of the interspaces near the cardiac apex This phenomenon may however be seen during the systole of a greatly enlarged heart without adhesions Systolic retraction may be seen posteriorly on the left side between the eleventh and twelfth ribs (Broadbent s sign) Pulsus paradoxus may be present If rheumatic fever is the etiologic factor a variety of valvular murmurs may be encountered

Only when valvular disease or hypertension coexists does one find the enormous cardiac enlargement referred to in the older textbooks *X-ray* and *fluoroscopy* may be of aid If during inspiration the heart rises especially if one side rises more than the other there is additional evidence for the diagnosis Bands of adhesions extending from the parietal pericardium to various intrathoracic structures are sometimes visualized by fluoroscopy or x ray

TREATMENT —Chronic constrictive pericarditis may be cured by pericardial resection in properly selected cases as suggested by Delorme Brilliant results from this operation have been secured within the past few years by surgeons specially skilled in thoracic surgery Medical treatment consists of the usual measures for combating myocardial insufficiency although digitalis is of no value and may be harmful The use of mercurial diuretics (1 to 3 cc of Salyrgan or Mercupurin intravenously) preoperatively and postoperatively may be life saving in the extremely edematous patient In adherent pericardium with external adhesions Brauer has advocated the resection of several ribs and costal cartilages overlying the pericardium in order that the heart may pull against yielding rather than rigid structures This procedure is palliative rather than curative

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PERICARDIAL DISEASES AS A CAUSE OF ACUTE CARDIAC COMPRESSION

BECK has described a triad which characterizes acute cardiac compression ' (1) A rising venous pressure (2) a falling arterial pressure (3) a small quiet heart The principal causes for acute cardiac compression are penetrating wounds of the chest causing laceration of the heart or coronary vessels and extravasation of blood into the pericardial cavity Other causes are rupture of a myocardial infarct of an aortic aneurysm a dissecting aneurysm or rupture of a contusion of the myocardium Rapidly developing effusions or the formation of gas within the pericardial cavity also cause acute cardiac compression

The condition is characterized in its early stage by weakness of the pulse and often pulsus paradoxus The skin is pale cold and clammy and the heart sounds are weak The veins may not be conspicuously dis

tended but measurement of venous pressure shows definite elevation above the normal Treatment depends upon the cause of the compression In cases of cardiac laceration immediate operation and suture of the site of hemorrhage is frequently life saving and is superior to expectant treatment as shown by the results of cases treated by both

cordial pain tachycardia dyspnea and occasionally cyanosis Electrocardiographic changes in the T waves and RS T segments may occur in either tamponade or myo cardial contusion resembling the changes de scribed under Acute Fibrinous Pericarditis

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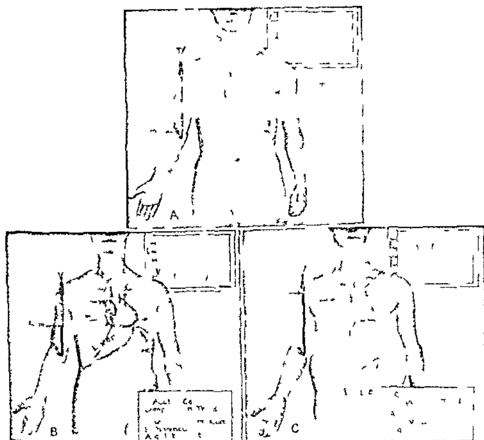


Fig 118—Cardiac compression triads For comparison normal (*A*) acute (*B*) and chronic (*C*) The acute compression is produced by fluid in the pericardial cavity Note collapse of the venous gateway and distention of the veins outside the pericardium The ventricles are shrunken and the heart *per se* is smaller than normal The parietal pericard um has not had time to dilate nor has there been sufficient time for the liver to en large and for ascites to form In the illustration for chronic compression of the heart the compression is pro duced by scar tissue The heart is a small shrunken organ in contradistinct on to cardiac dilatation The veins dilate in response to the high venous pressure The liver and spleen enlarge and ascites develops (Beck, C S J A M A *104* 714 1935)

methods at the Cincinnati General Hospital Contusion of the heart following penetrating or non penetrating injuries to the chest occasionally produces pericardial effusion and compression Even in the absence of effusion cardiac contusion resembles and must be differentiated from cardiac tam ponade The diagnostic features of cardiac contusion *include* thoracic trauma pre

OTHER CONDITIONS AFFECTING THE PERICARDIUM

Pneumopericardium — Pneumopericar dium resulting from the presence of gases in the pericardium is a rare condition This condition may follow penetrating wounds an infection caused by gas forming organ isms rupture of a hollow viscus or rupture of the lung into the pericardium

When pneumopericardium is present, relative cardiac dulness is replaced by tympany, and if a fluid exudate collects peculiar splashing and churning sounds are audible On x ray examination the air within the pericardium is apparent If the fluid is purulent or pneumocardiac tamponade develops, drainage is indicated

Hydropericardium — Hydropericardium is that condition in which a transudate collects in the pericardial cavity In many chronic disorders especially cardiac and renal disease a slight excess of fluid (25–200 cc) may be found at autopsy

Hydropericardium *per se* causes no symptoms except in rare instances when an excessive amount of fluid develops In such cases the usual signs found with pericardial effusion appear and paracentesis may be necessary

Calcified Pericardium —When any inflammatory exudate about the heart becomes organized, lime salts may be deposited Such calcification of the pericardium most commonly follows tuberculous and pneumococcus pericarditis The extent of the calcification is variable, in some instances it involves the entire pericardium The signs of chronic constrictive pericarditis may be found More often the condition is found at autopsy or by x ray examination and is of no clinical significance *per se*

Tumors of the Pericardium —Primary neoplastic disease of the pericardium is extremely rare Secondary invasion by carcinoma malignant lymphoblastoma melanoma or fibrosarcoma may occur

Congenital Pericardial Defects —Rarely the parietal pericardium is absent This results in unusual mobility of the heart, and pain and sudden death have been reported with this condition owing to sudden kinking of the great vessels as a complication of excessive cardiac mobility

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DISEASES OF THE MYOCARDIUM

DISEASES of the myocardium may be divided into the acute and the chronic forms The term *myocarditis* has been applied to both forms but it seems unsuited to the chronic types in which the pathologic process is more commonly degenerative than inflammatory With rare exceptions all of the diseases of the myocardium are secondary to local or general diseases The primary disease may be infectious, toxic or of unknown cause such as hypertension or arteriosclerosis These result directly or indirectly in alterations in the heart muscle which may or may not produce anatomic change that is demonstrable after death but which during life gave rise to symptoms due to impairment of the heart s efficiency as a pump Dilatation and hypertrophy of the heart are fundamental changes nearly always present in myocardial disease

Dilatation —When the normal ventricle is made to eject blood against a greater resistance than that to which it is accustomed or when the contractile power of the ventricle is impaired while the resistance remains normal strain of the heart sets in Under such conditions the ventricle tends to reduce its systolic discharge, the blood which consequently remains in it when added to that which enters during diastole increases the diastolic volume and raises the initial tension to which the muscle is subjected It is a cardiac law that increased lengthening and stretching increase the irritability and contraction so that the systolic output in relation to diastolic inflow is restored to normal This capacity for adaptation is large in a healthy person but is limited or even lost in the presence of disease or impairment of myocardial integrity or efficiency so that pathologic dilatation develops readily and leads to congestive heart failure In cardiac failure the heart is no longer able to

discharge as much blood as it receives and venous pressure rises throwing added strain on the myocardium Dilatation may result then from two causes passive distention when the elastic resistance of the myocardium is overcome by increased initial intraventricular pressure, and diminution of tonus which allows the ventricle to accommodate an increased volume of fluid without raising the initial tension necessary to increase the strength of its beat

Hypertrophy is a compensatory phenomenon by which the diameter of the muscle fibrils is increased The nature of the responsible stimulus is unknown but both experimental and clinical evidence indicates that it is a physiologic reaction to continued overwork Starling s law states ' that the mechanical energy set free in passing from the resting to the contracted state depends on the area of chemically active surfaces *i.e* on the length of the muscle fibers Although the thicker and longer muscle fibers of the enlarged heart are mechanically advantageous they work under chemical and physiochemical disadvantages which lead them to fail under strain more readily than fibers of normal size Their hypertrophy is not accompanied by a proportional increase in their blood supply that is in oxygen and nutrition and this contributes to their easier exhaustibility The dilated and hypertrophied heart is therefore one that has a limited reserve

It follows from these considerations that enlargement of the heart may result from a variety of factors and may be expected to predominate in that chamber which is subject to the greatest mechanical strain Thus necropsy generally reveals preponderant enlargement of the right side of the heart in patients whose hearts failed as the result of interference with blood flow through the pulmonary circuit Such a condition is likely to be found in chronic emphysema long standing asthma pulmonary fibrosis stenosis of the pulmonic valve and other conditions It is often called *Cor Pulmonale* In the higher degrees of mitral stenosis enlargement of the left auricle is likely to be predominant but this is very often associated with much enlargement of the right ventricle or the whole right heart Conversely in systemic hypertension aortic valve lesions coarctation of the aorta and so on left sided enlargement generally shows significant dominance It must be remembered that the heart arteries and veins form a complete circuit so that alterations in flow originating in one portion are certain to be reflected by secondary alterations in the others Hence in most cases of heart failure all of the chambers of the heart are generally involved to a greater or lesser extent in the process of dilatation and hypertrophy

Congestive heart failure is described elsewhere but in view of the foregoing paragraph it should be mentioned that such failure may also be dominantly one-sided may result from failure of both sides or may begin as one sided and rapidly become generalized *Failure of the right heart* is manifest clinically by increased pressure stasis and congestion in the systemic veins The veins are visibly distended there is enlargement of the liver renal congestion causes albuminuria and oliguria splanchnic congestion produces digestive disorders edema pleural effusion and ascites develop *Left heart failure* leads to venous stasis and congestion in the pulmonary circuit This produces dyspnea orthopnea and cough along with cyanosis and owing to the relative lesser strength of the right heart secondary dilatation and failure are prone to follow shortly resulting in the commonest clinical picture that of generalized cardiac failure

Acute Myocarditis —*Definition* —Acute myocarditis is an acute inflammation of the walls of the heart

Incidence —The disease occurs at all ages and in both sexes It is commonest in childhood and early adult life and is comparatively rare in individuals more than forty The frequency with which acute myocarditis occurs cannot be stated because it often runs its course without producing any symptoms which make diagnosis possible The clinical diagnosis is sometimes made erroneously no myocardial lesions being found at autopsy

Etiology —Acute myocarditis is probably always secondary It may be caused by any of the acute infections but occurs most frequently in acute rheumatic fever diphtheria influenza typhoid fever scarlet fever smallpox erysipelas septicemia pyemia

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DISEASES OF THE MYOCARDIUM

DISEASES of the myocardium may be divided into the acute and the chronic forms The term *myocarditis* has been applied to both forms but it seems unsuited to the chronic types in which the pathologic process is more commonly degenerative than inflammatory With rare exceptions all of the diseases of the myocardium are secondary to local or general diseases The primary disease may be infectious toxic or of unknown cause such as *hypertension* or arteriosclerosis These result directly or indirectly in alterations in the heart muscle which may or may not produce anatomic change that is demonstrable after death but which during life gave rise to symptoms due to impairment of the heart s efficiency as a pump Dilatation and hypertrophy of the heart are fundamental changes nearly always present in myocardial disease

Dilatation —When the normal *ventricle* is made to eject blood against a greater resistance than that to which it is accustomed or when the contractile power of the ventricle is impaired while the resistance remains normal strain of the heart sets in Under such conditions the ventricle tends to reduce its systolic discharge the blood which *consequently remains in it* when added to that which enters during diastole increases the diastolic volume and raises the initial tension to which the muscle is *subjected* It is a cardiac law that increased lengthening and stretching increase the irritability and contraction so that the systolic output *in* relation to diastolic inflow is restored to normal This capacity for adaptation is large in a healthy person but is limited or even lost in the presence of disease or impairment of myocardial integrity or efficiency so that pathologic dilatation develops readily and leads to congestive heart failure In cardiac failure the heart *is no longer* able to

easily compressible and reflects the irregularity of the heart The blood pressure is usually diminished and the systemic veins are collapsed The apex impulse is diffuse displaced to the left and may be feeble when palpated The heart is usually dilated and when this is marked the area of cardiac dulness is enlarged and systolic murmurs may be present at the base or apex or over the whole heart The sounds are often slapping and the first sound is likely to be of poor quality These symptoms are due chiefly to a circulatory failure of vasomotor origin

When CONGESTIVE HEART FAILURE sets in the usual symptoms of passive venous congestion and deficient circulation develop cyanosis dyspnea orthopnea and cough and the veins of the neck are full There may be nausea and vomiting with a sense of fulness and pain in the epigastrium and right hypochondrium Dependent edema begins to appear and the urine becomes scanty and contains albumin and casts With these symptoms there are moist rales and impaired voice and breath sounds with diminished resonance at the base of the lungs or evidences of pleural effusion especially on the right side The liver may be considerably enlarged by congestion its lower border may extend down to the umbilicus and it may pulsate with systole There is marked tenderness in the hepatic region Ascites may develop These are all symptoms common to cardiac failure and are in no way peculiar to acute myocarditis but when they occur during or shortly after an acute infection in a patient whose heart was previously normal the diagnosis of acute myocarditis can be made with reasonable assurance

The clinical picture is often that of a combination of the phenomena of peripheral vascular failure with those of congestive heart failure

FEVER is common but is often masked by that due to the primary infection It is usually moderate (seldom above 103° F) and may be continuous or intermittent Moderate leukocytosis may occur with or without a relative increase in the polynuclear cell count but a normal count or even leukopenia is quite as *frequent* The red cell sedimentation rate is usually increased The increase is likely to persist as long as the inflammatory process remains It is commonly a more sensitive and trustworthy guide to healing than either leukocytosis or differential white cell counts There is usually moderate secondary anemia

RHEUMATIC MYOCARDITIS occurs to some extent in probably not less than 90 per cent of all patients with acute rheumatism The myocardial changes however in the majority of cases are slight and often transitory or heal without leaving clinical evidence of their existence Such slight involvement usually passes unrecognized unless special search is made In the more pronounced cases, the usual signs and symptoms are those just described Impulse conduction is frequently delayed This is recognizable only when graphic records are made because the heart block is seldom sufficient to cause dropped beats Premature contractions and nodal rhythm are very common but more serious arrhythmias such as auricular fibrillation are rare in the acute stage of rheumatic myocarditis Tachycardia is the rule although bradycardia may be encountered as a rare and usually grave symptom Rheumatic endocarditis and pericarditis very frequently accompany myocarditis and render its recognition difficult in many cases

DIPHTHERIA is complicated by myocarditis fairly often especially when the use of antitoxin has not been adequate or early This form of myocarditis may be slight and cause few symptoms but when diphtheria is severe or its treatment has been neglected the myocarditis is likely to be very severe and often rapidly fatal Even in patients with few or no recognizable cardiac symptoms the heart may be so extensively damaged that moderate exertion may cause collapse or sudden death The heart is dilated the pulse is feeble and readily compressible and the patient is easily exhausted A systolic murmur due to a relative mitral insufficiency is common Tachycardia is the rule in the first few days and sinoauricular block or premature contractions are frequent Bradycardia is more likely to occur in this form of myocarditis than in any other and is of gravest significance for it indi*cates extensive damage to the conduction* system with consequent severe heart block

and malaria It may result from direct invasion of the heart by the infecting organisms or from the action of their toxins which reach the heart through the blood stream Phosphorus arsenic chloroform and other poisons may also be causes as may severe degrees of thyrotoxicosis *Fiedler's myocarditis* is an acute or subacute form of unknown etiology occasionally seen in adults This is also called *idiopathic myocarditis* Acute myocardial infarction produces a localized area of acute degenerative myocarditis

Morbid Anatomy—The lesion may be a diffuse parenchymatous degeneration Grossly this appears as cloudy swelling of the muscle and microscopically as a granular change in the sarcoplasm of the muscle cells which may more or less obscure the striations This lesion is usually due to the action of bacterial or other toxins It may undergo complete resolution More commonly the lesions are focal in the interstitial tissues or around the blood vessels Between the muscle fibers there may be infiltration of round cells leukocytes and an albuminous exudate The muscle fibers undergo albuminous degeneration and lose their markings or show evidence of hyaline or fatty degeneration Infiltrations of round cells frequently occur beneath the pericardium and the mural endocardium so that these membranes are involved with the myocardium and the condition becomes pathologically carditis rather than pure myocarditis The destroyed muscle cells may be absorbed gradually and replaced by fibrous scar tissue These lesions are usually microscopic but occasionally they may produce scars visible to the naked eye

In some cases the chief or only lesion is an acute interstitial productive myocarditis This manifests itself as a primary increase in the cells of the fixed connective tissue and adventitia of the vessels with invasion of lymphocytes plasma cells and eosinophilic leukocytes Healing results in the formation of multiple minute scars which are very difficult to discover

A rare form of myocarditis occurs in sepsis and pyemia when bacterial emboli lodge in the finer arteries of the heart This may produce one or many abscesses A single large abscess may involve the entire thickness of the ventricular wall and may cause sudden death by rupture or may heal and leave a thin wall of fibrous tissue which bulges and forms a cardiac aneurysm

Rheumatic myocarditis is accompanied by characteristic lesions known as *Aschoff's nodules* These are submiliary collections of large spindle shaped or branching cells with large sometimes multiple nuclei They probably arise from the connective tissue and are accompanied by collections of lymphocytes and eosinophilic leukocytes They occur in the interstitial tissues usually around the blood vessels and just beneath the endocardium The interventricular septum is frequently involved and invasion or destruction of portions of the conducting system often produces varying grades of heart block The nodules are seldom visible on gross examination but are readily seen under the microscope They occur only in rheumatic fever but cannot always be demonstrated even in proved cases Parenchymatous and interstitial myocarditis may accompany the nodules

Diphtheritic myocarditis is due to the action of the toxin upon the heart muscle In most instances the heart muscle is flabby and edematous and especially where heart block is present there is an interstitial infiltration of polynuclear cells and lymphocytes in the region of the bundle of His If the damage is not too extensive the destroyed muscle cells are absorbed and replaced by scar tissue which is widely distributed and usually not grossly apparent

Symptoms—The onset of acute myocarditis rarely can be determined with accuracy because the condition usually develops during or immediately after an acute infection There are no characteristic symptoms but the condition is to be suspected if circulatory disturbances appear during or following acute infection Even under such circumstances diagnosis can seldom be made with certainty The symptoms of myocarditis may not develop for several weeks after subsidence of the acute infection

ACUTE MYOCARDITIS often causes anxiety and a sense of oppression or pain in the chest especially in the precordial region The *heart action* is usually disturbed the rate is rapid and any of the forms of irregularity may appear Bradycardia is an occasional manifestation The pulse is soft small

may be dangerous in peripheral vasomotor failure by diminishing further the already constricted vascular bed as well as the output of the heart Epinephrine is sometimes of value when administered slowly and continuously in the form of intravenous drip 1 cc of the 1 1000 solution being added to each liter of a 5 per cent solution of dextrose in normal saline solution From 1 to 3 liters may be injected slowly within twenty four hours Glucose given by rectum or clysis is valuable as a supportive measure at times The use of an ice-bag over the heart may be of some value and at least insures periods of complete quiet to keep it in position

During *convalescence* rest should be continued until the heart rate remains normal and the more serious disturbances of rhythm have disappeared Massage passive and later mild active movements should be begun before the patient is permitted to sit up Sitting up should be allowed for only a few minutes at first and the time very gradually increased The patient should not be permitted to get out of bed until he can sit up in bed without fatigue for several hours A nutritious easily digestible diet adequate in vitamins should be given Iron may be useful to combat anemia When the patient can be up and about a very gradual course of physical training may be instituted but in the more serious cases marked exertion cannot be allowed for several months

Chronic Myocardial Disease—Several types of chronic disease of the myocardium are generally described the differentiation being made on the basis of the pathogenesis or of the pathologic changes in the heart muscle This division may be reasonably satisfactory to the pathologist but from the clinical point of view it does not seem to serve any useful purpose because the majority of cardiac symptoms and signs are common to all types irrespective of pathology or pathogenesis The separate clinical discussion of each of these types has tended to confuse the minds of both students and physicians since however distinct they be pathologically they constitute symptomatically but a single syndrome The inclusion of the several types under the single title of *chronic myocardial disease* on the other hand serves to emphasize their clinical unity This plan of presentation simplifies the entire subject of chronic disease of the heart muscle and obviates much unnecessary repetition

Incidence.—Chronic myocardial disease occurs more frequently in men than in women (about 3 to 2) One third of all cases occur between the ages of fifty-one to sixty while three fourths of all are found in the three decades between forty-one and seventy years These figures are for conditions without structural lesions of the valves When those with organic valve lesions are included the age of greatest incidence is lowered by the large rheumatic group in which myocarditis accompanies the more evident endocarditis

Morbid Anatomy and Pathogenesis—CHRONIC MYOCARDITIS—The term 'chronic myocarditis has been used loosely to designate most or all of the conditions included by the term chronic myocardial disease' The term myocarditis should however be restricted to those conditions in which there is a productive inflammatory process in the heart muscle in contradistinction to those in which the lesion is essentially degenerative Chronic myocarditis may develop as a late stage of the acute process or may occur without previous evidence of the acute form The most common *acute infections* which cause it are acute rheumatic fever typhoid fever influenza the septicemias and occasionally diphtheria Chronic myocarditis of some degree is almost always associated with the various forms of chronic or subacute endocarditis and is often the most important cause of the cardiac symptoms in such cases

Gross examination of the heart reveals hypertrophy and dilatation and in some instances evidence of an increase in the quantity of fibrous tissue Microscopically there is round cell infiltration in the interstitial tissues and parenchymatous degeneration of the muscle fibers in areas where the process is active In older lesions there is connective-tissue proliferation and degeneration of the muscle cells which are ultimately replaced by fibrous scar tissue The latter process may end in healing but in many cases the processes are progressive or the inflammation undergoes remissions and exacerbations Chronic myocarditis may finally develop in a heart which is already the seat of old healed lesions remaining from an earlier at

This symptom may develop suddenly during convalescence from diphtheria, and is to be anticipated when tachycardia persists beyond the fourth or fifth day It is rapidly fatal in the majority of cases Studies by Burkhardt Eggleston and Smith indicate that the presence of changes in the electrocardiogram particularly increasing delay in the conduction time is of greater value in the early diagnosis of this condition than are any of the clinical findings

Diagnosis of acute myocarditis is always difficult and sometimes impossible In many cases it is little more than an inference based on the conditions under which the symptoms have developed The diagnosis at best is usually one of probability only and must often be reached mainly by a process of exclusion Acute myocarditis is not infrequently seen after death in patients who have had no symptoms from which a diagnosis could be made during life

Feeble, rapid pulse low blood pressure weakness exhaustion digestive disturbances restlessness and anxiety are produced in acute infections by *circulatory failure of vasomotor origin* as well as by acute myocarditis Differential diagnosis of their cause is often impossible Dilatation of the left ventricle may cause relative insufficiency of the mitral valve The signs of this type of insufficiency are the same as those evoked by mitral endocarditis Inasmuch as endocarditis is a common accompaniment of acute myocarditis especially in rheumatic fever differentiation between the two forms of mitral incompetence is often difficult

Course and Prognosis —Acute myocarditis may be very mild and permit early and complete recovery or so extremely severe that it is fatal within a few days Death is most likely to ensue in the septic and diphtheritic types The intensity of the clinical manifestations may not be a true index of the ultimate prognosis Patients with few and slight symptoms may succumb rapidly while others with marked clinical symptoms may recover gradually and suffer little permanent functional impairment of the heart Partial recovery is common the heart remaining permanently damaged to a considerable extent or the myocarditis may become chronic The physician should always therefore be guarded in giving a prognosis either as to probable duration or ultimate outcome

Treatment should begin with efforts to prevent the development of acute myocarditis in every patient with one of the probable causative infections The patient should be kept at complete rest in bed until all evidences of active infection have disappeared Where the infection has been severe or of long duration this should continue well into convalescence In acute rheumatic fever the patient should not be allowed to sit up in bed until the temperature has remained normal for at least two weeks and the red cell sedimentation rate has fallen to normal When cardiac symptoms have been present this period should be lengthened The early and adequate administration of antitoxin is the most effective means of preventing the development of diphtheritic myocarditis This should be combined with the measures just outlined

The treatment of acute myocarditis itself consists primarily in securing *maximum rest for the heart* along the lines set forth in the foregoing paragraph During the active stage the patient must be confined to bed The use of the bed pan and urinal must be insisted upon and the subject should not even feed himself and must not sit up in bed All forms of mental excitement must be avoided and abundant sleep secured by the use of bromides and simple sedatives *Drug therapy* is not called for unless there be evidence of cardiac failure Cardiac stimulants may then become necessary Strychnine and alcohol have their advocates but there is no satisfactory evidence that they are of any real value The administration of oxygen may enhance the patient s comfort and perhaps the chance of recovery Digitalis which is a most valuable agent in the treatment of chronic cardiac disease is usually useless in acute myocarditis and may be dangerous It is best to omit it entirely If tried it should be administered in small doses (0 1 Gm [1½ grains] of the leaf three or four times daily) and a close watch maintained for unfavorable effects Caffeine and theobromine are often better stimulants in such conditions and are best given subcutaneously in the form of one of their soluble preparations Intramuscular injection of epinephrine (adrenalin) is rarely of value and

degeneration It often appears in chronic valvular disease with other evidences of chronic myocarditis and may be produced by prolonged infections and by chronic poisoning with phosphorus arsenic and chloroform it occurs very commonly in severe anemia The heart may appear almost normal grossly it may be flabby and yellowish in color In severe anemia small patches or strips of yellow may be visible beneath the endocardium especially in the papillary muscles and the trabeculae (tiger heart) The fat is probably deposited in the heart to replace destroyed muscle tissue and comes from without rather than from within the heart itself

FATTY INFILTRATION or the FATTY HEART is a part of general obesity and is said to be especially common among excessive beer drinkers In this condition the heart is encased in an excessively thick layer of subpericardial fat This often penetrates into the myocardium between the muscle bundles and may even cause degeneration and destruction of some of them The heart is usually somewhat dilated and hypertrophied The only symptoms are those of heart failure in an obese patient

Symptoms of chronic myocardial disease not infrequently appear in exophthalmic goiter and toxic adenoma of the thyroid The frequency and extent of structural change in the myocardium in these disturbances has not been adequately studied The left ventricle and later the whole heart may undergo hypertrophy and dilatation Patchy or diffuse thickening of the endocardium may occur and at times extend into the adjacent muscle There may be some lymphocytic infiltration of the myocardium Structural changes may be wholly lacking This is evidenced clinically by the fact that relief of the thyrotoxicosis is often followed by prompt and lasting disappearance of all evidences of cardiac involvement Myxedema may be accompanied by symptoms of myocardial insufficiency and an enlarged heart There are however no specific pathologic changes to be found other than coronary sclerosis and some parenchymatous degeneration of the muscle Myxomatous degeneration is rare

The prolonged excessive physical exertion required of professional athletes and certain classes of laborers has been thought to cause hypertrophy and chronic myocardial damage Studies by Gordon Levine and Wilmaers on a series of Marathon runners failed however to reveal cardiac enlargement even in men who had engaged in the most vigorous physical effort for many years It seems probable that physical exertion alone does not cause myocardial damage in the absence of infection vascular changes or other disease

BERIBERI HEART (vitamin B deficiency) has been thought by Weiss and his associates and earlier by Wenckebach to be a definite clinical entity accompanied by manifestations of myocardial insufficiency low blood pressure and enlargement of the heart especially of the right side There are no specific pathologic changes though there may be some hydropic degeneration of the muscle fibers along with other nonspecific changes The diagnosis is a clinical one and rests upon the preceding phenomena found in a patient with a history of gross deficiency of vitamin B in his diet or with clinical beriberi as revealed by symptoms The diagnosis is felt by some to be confirmed by favorable response to the administration of thiamine chloride or the vitamin B complex which may have to be given parenterally The electrocardiogram in beriberi heart disease is characterized mainly by low voltage of the QRS and the T waves

Symptoms —Chronic myocardial disease may produce no symptoms whatever and may even be the cause of sudden death in apparently healthy individuals Careful examination will in most cases however reveal abnormalities which are sufficient to establish the probable diagnosis Close questioning also brings to light symptoms indicative of some impairment of cardiac efficiency which the patient often considers unimportant such as moderate shortness of breath following stair climbing walking against a high wind or running a short distance Some degree of hypertrophy and dilatation is almost invariably associated with chronic myocardial disease even when there are no symptoms This should be found in the course of routine examination especially if this includes fluoroscopic study and should arouse suspicion of chronic disease of the heart muscle Occasionally fibrillation of the

tack The changes are least marked in the auricles and usually best developed in the left ventricle

Syphilis.—Despite its frequent involvement of the aorta syphilis is rarely a direct cause of chronic myocarditis by virtue of invasion of the myocardium by the *Treponema* It may produce solitary or multiple gummata but even these lesions are rare *Chronic focal infection* in the teeth, tonsils sinuses gallbladder or elsewhere may occasionally be a cause It is difficult and often impossible however to establish any relationship between chronic myocarditis and such disturbances *Tuberculous myocarditis* is extremely rare except in association with tuberculous pericarditis or general miliary tuberculosis In both conditions the myocarditis is masked by the symptoms of the underlying tuberculous process

Fibrosis of the Myocardium (Interstitial Myocarditis) —This is by far the commonest form of chronic myocardial disease and is usually the result of arteriosclerosis of the coronaries generalized arteriosclerosis syphilitic coronary ostial stenosis or arterial hypertension Each of these conditions may cause destruction of muscle fibers from impairment of the circulation to the heart The muscle fibers become fragmented lose their nuclei and may ultimately be replaced by new fibrous tissues The interstitial fibrous tissue may also proliferate Scars are thus formed in the myocardium When a coronary artery is narrowed at its mouth or in one or more of its main branches the lesion is more or less diffuse in the entire area which it normally supplies when one or more small branches are chiefly affected or completely occluded by thrombi the process is focal The occlusion of a medium sized branch results in myocardial infarction with destruction which may involve the entire thickness of the ventricular wall Healing produces a fibrous scar which is called a 'myocardial cicatrix If large this may stretch gradually and bulge with the production of a cardiac aneurysm Hearts with this type of degeneration are dilated and hypertrophied The fibrosis may not be visible to the naked eye or small whitish areas of fibrous tissue scattered throughout the ventricular musculature may be apparent on close examination Such areas are most commonly found near the apex of the left ventricle and in the papillary muscles but they may appear anywhere The focal lesions are usually readily visible as grayish white patches beneath the endocardium and within the ventricular wall on section

Chronic myocardial disease due to *hypertension* causes fairly characteristic pathologic changes There is marked hypertrophy of one or both ventricles with extensive dilatation Some of the largest hearts are found to be the result of prolonged hypertension Macroscopically the muscle appears essentially normal but microscopically there may be diffuse proliferation of connective tissue within and between the muscle bundles or there may be no evidence of pathologic change other than hypertrophy The auricles are much less affected than the ventricles They are usually dilated however and at times undergo considerable hypertrophy The condition known as *essential hypertension* and the hypertension associated with *chronic nephritis* are the two great causes of this type of myocardial degeneration and are regarded by some as the commonest causes of chronic myocardial disease in general The left side of the heart is predominantly affected but in the later stages right sided dilatation and hypertrophy are usually also found Involvement may be limited chiefly to the right ventricle and auricle in congenital pulmonary stenosis in long standing bronchial asthma or pulmonary emphysema and under other conditions in which there is continued hypertension in the pulmonary circuit

Autopsy sometimes reveals no pathologic changes in the myocardium other than dilatation or hypertrophy yet the patient may have presented during life a typical picture of congestive heart failure The failure in such cases seems best explained on the theory of a gradual exhaustion of the dilated and hypertrophied ventricular muscle as the result of prolonged overwork combined with the physiologic disadvantages under which the hypertrophied muscle fibers have been compelled to labor A relative physiologic inefficiency has led to a final functional insufficiency with exhaustion and death

MISCELLANEOUS CONDITIONS —Fatty degeneration is frequently one of the pathologic changes associated with chronic myocardial

block causes dropping of the beats which can be differentiated from premature beats by the silence of the heart during a period nearly equal to that of two normal cycles In partial or complete block the ventricular rate may suddenly fall so low as to cause temporary cerebral anemia The patient goes into syncope and often has a convulsion (Adams Stokes syndrome) The electrocardiogram may show the presence of some degree of intraventricular block

The *heart sounds* are altered in various ways They are often diminished but may be loud and have a slapping quality If systemic blood pressure is much elevated the second aortic sound is accentuated The pulmonic second sound is accentuated by increased pressure in the pulmonary circulation with or without signs of passive congestion of the lungs The first sound at the apex may be increased when there is ventricular hypertrophy or it may be diminished and of poor muscular quality in dilatation It is sometimes impure and often split Reduplication of either sound may cause a gallop rhythm

Murmurs may or may not be present They are due to an associated valvular lesion caused by preceding endocarditis valvular sclerosis or to extensive dilatation of the heart with resulting functional incompetence of the valves Differentiation between their causes is difficult and may be impossible Dilatation of the left heart often produces functional mitral incompetence evidenced by signs identical with those of incompetence due to mitral endocarditis Rarely extreme dilatation renders the aortic valves incompetent by stretching the aortic ring Incompetence of the tricuspid valve occurs frequently when the right heart is dilated It may produce the typical systolic murmur over the lower end of the sternum but a murmur is often absent or is obscured by the systolic murmur of mitral insufficiency With marked relative tricuspid insufficiency the neck veins are full and show a ventricular type of pulsation With this the liver is enlarged usually tender and often shows an expansile pulsation with cardiac systole

The *physical signs* in the cardiovascular system vary greatly Some enlargement of the heart is almost invariably present because of hypertrophy and dilatation Since it is rarely possible to determine by physical examination which of the two factors predominates it is customary to use the inclusive term enlargement In the presence of failure however, dilatation may be assumed to be in the ascendency The extent of enlargement varies, although it is pronounced in the majority of cases The apical impulse is usually forcible and often heaving when there is great hypertrophy, marked dilatation on the other hand usually renders it diffuse and feeble The lower outer point of the apex impulse is the most trustworthy clinical evidence of enlargement of the heart

The most important symptoms of chronic myocardial disease are those due to congestive heart failure or to the anginal syndrome For clarity as well as emphasis they are accorded separate descriptions

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CONGENITAL AFFECTIONS OF THE HEART

Definition—In the course of intra uterine life anomalies in the position and structure of the heart or great vessels sometimes result from faulty development or disease Such defects comprising the congenital affections of the heart usually lead to disturbances in the circulation and give rise to abnormal physical signs

This group of conditions affects a relatively small number of individuals for it comprises only about 2 per cent of all cases of organic heart disease Many of the infants with such defects die during the first few days or weeks after birth The etiology is but imperfectly understood The distinction between congenital and acquired lesions as a rule is not difficult To date the only defect which has been repaired successfully by operation is patent ductus arteriosus

Etiology—Congenital affections of the heart are frequently associated with other

auricles may be unnoticed by the patient, a reduplicated first sound may be found, or pulsus alternans may be discovered during auscultatory determination of the blood pressure Finally, a routine electrocardiographic examination may reveal defects in conduction such as intraventricular block

Usually chronic myocardial disease evokes the common symptoms of heart failure or myocardial insufficiency These are not pathognomonic of the condition which causes the failure The number or severity of the symptoms varies greatly and *there is no* necessary relationship between their number or intensity and the nature or extent of the structural changes in the heart although certain syndromes are more characteristic of one type of myocardial disease than of others Anatomically slight lesions may cause severe symptoms especially if they involve the conduction system, while extensive damage of the ventricular musculature may produce only minor symptoms of impaired cardiac efficiency It is important to keep these facts always in mind if serious errors in diagnosis or prognosis are to be avoided

The *symptoms referable to the cardiovascular system* are few and relatively unimportant in most cases Palpitation fluttering or subjective precordial beating may accompany auricular fibrillation auricular flutter premature beats (extrasystoles) or marked enlargement of the heart There may be a sense of fulness in the precordial region fleeting pains or a dull heart ache and some precordial tenderness is not uncommon *Throbbing of the peripheral arteries* especially in the neck may occur with aortic insufficiency or hyperthyroidism but is uncommon otherwise and is unimportant

The NERVOUS SYSTEM is affected by the inadequate circulation which causes a sense of weakness or exhaustion and drowsiness Sleeplessness may occur and hallucinations or delirium may develop The memory is often impaired and mental effort may cause severe fatigue

CYANOSIS is the rule but it is often slight and may be absent Pallor is frequent and in the late stages the skin and sclerae may be icteric Digestion is usually impaired the appetite is poor or lost and gaseous distention is often a prominent and troublesome symptom Nausea and vomiting are rather common as the result of congestion in the splanchnic area They may be associated with pain and soreness in the epigastrium and right hypochondrium which is usually due to more or less acute congestion and swelling of the liver

KIDNEY FUNCTION is impaired, oliguria is often marked and the urine is concentrated and of high specific gravity It may be dilute with a low and fixed gravity when there is an associated nephrosclerosis It may contain considerable albumin and all types of casts except the waxy The excretion of phenolsulfonphthalein may be as low as 15 to 30 per cent With the impaired renal function nitrogenous waste products may be retained in the blood but this is seldom marked

The *heart rate* is commonly increased even during rest Auricular fibrillation is present in the majority of cases This may be transitory or paroxysmal but is generally permanent The rate of the ventricles is usually rapid (120 or more beats per minute) and there is total irregularity of the beats both in force and in rhythm The rate varies from minute to minute and is peculiarly subject to marked acceleration after exertion Many of the ventricular beats are too feeble to transmit a wave to the wrist so that the radial pulse rate is usually less than that of the heart This difference is called the *pulse deficit* and its degree is usually more or less parallel to the degree of cardiac failure The radial pulse rate must never be considered an index of the heart rate in fibrillation

AURICULAR FLUTTER is comparatively uncommon PREMATURE VENTRICULAR BEATS (extrasystoles) are often present if the heart rate is not very high They are characterized by their prematurity and by the long subsequent diastole The premature systole can be heard over the heart but sometimes cannot be felt in the pulse Premature beats have relatively little significance unless they are very numerous They may then contribute to the embarrassment of the circulation *Complete heart block* is not infrequent especially in cases with extensive coronary sclerosis It is easily recognized by the very slow heart rate (below 40 per minute) the rhythm being regular *Incomplete*

great vessels or abdominal viscera There is sometimes complete *situs inversus* Transposition of the large arterial trunks is likewise not uncommon If unassociated with structural defects dextrocardia may give rise to neither symptoms hypertrophy cyanosis nor heart murmur and may be accidentally discovered in the course of a physical examination

Anomalies of Structure—Structural anomalies may result from incomplete development of certain parts of the heart such as one of the septa from fetal endocarditis or from persistence of fetal conditions such as the foramen ovale or ductus arteriosus (Botalli)

Pulmonic Stenosis—Narrowing of the pulmonic orifice is one of the commonest forms of congenital heart disease It was formerly regarded as being often the result of fetal endocarditis but is now usually believed to be due to a failure of proper development of the infundibulum of the right ventricle

The stenosis varies in degree depending in a measure on whether it is located in the muscle of the ventricle in the infundibular region or in the valvular ring Usually there is an associated defect in the ventricular or auricular septum or a patent ductus arteriosus A frequent combination is stenosis of the infundibulum of the right ventricle and of the pulmonary valve defect in the interventricular septum dextroposition of the aorta and enlargement of the right ventricle (tetralogy of Fallot) The patency of the septum or ductus is to be regarded as a compensatory mechanism for relieving the heightened pressure within the right ventricle

Pulmonic Atresia—Obliteration of the pulmonic orifice is a less frequent but more serious lesion than pulmonic stenosis The pulmonary artery is very small and there may be persistence of the ductus arteriosus together with patency of the foramen ovale or defect in the ventricular septum

Pulmonic insufficiency is relatively rare It is usually due to fetal endocarditis

Tricuspid or mitral defect is uncommon Stenosis or atresia is more frequently seen than insufficiency

Anomalies of the Cardiac Septa—(1) Defect in the Interauricular Septum—Patent foramen ovale is a frequent congenital defect, commonly found in association with pulmonic stenosis or an imperfect ventricular septum The membrane closing the foramen ovale may fail at one point to become attached to the ring about it leaving a valvelike slit Neither this opening nor small fenestrations which may occur in the membrane are of any clinical significance and are not infrequently encountered in necropsies on persons who have died of various unrelated affections

(2) Defect in the Interventricular Septum—A defect in the interventricular septum (Roger s disease) is one of the common congenital lesions and in about half the cases is associated with pulmonic stenosis The opening between the ventricles under such circumstances acts as an escape valve for the overloaded right heart The defect is usually in the upper part of the septum If the septa of both auricles and ventricles are lacking the heart consists of only two chambers as in fish If in the absence of the ventricular septum the auricular septum is present the heart is composed of three cavities—*cor triloculare* Defect of the membranous septum when the only lesion present is not incompatible with a long and fairly active life Such was the case in the instance of Professor Brooks of the Johns Hopkins University who although he knew from early manhood that he had heart trouble accomplished an extraordinary amount of work and lived to be about sixty (Osler)

Patent Ductus Arteriosus—An open ductus Botalli is comparatively rare as a solitary lesion about two thirds of the cases have other congenital cardiac defects as well This fetal vessel however frequently remains patent in the presence of pulmonic stenosis usually in combination with a defect in one or both septa The blood may thus reach the lungs by an accessory channel when the pulmonic orifice is narrowed The persistence of the ductus arteriosus is often necessitated by other structural changes in the heart

Coarctation of the Aorta—When the ductus arteriosus shrinks the aorta sometimes becomes narrowed or completely occluded at the point of juncture The condition is often overlooked for it is compatible

forms of imperfect development notably mental deficiency They are said to occur more often in firstborn children than in later ones The causes of defective growth are not known Occasionally it appears that heredity plays a part in that such anomalies may appear in direct or collateral line for several generations Consanguinity is regarded as an important factor in exerting this hereditary influence Instances have been recorded in which infections in the mother during pregnancy particularly rheumatic fever and syphilis have been followed by the birth of children with imperfect hearts, although the association between cause and effect has not been definitely established

Fetal endocarditis is probably responsible for valvular deformities in a small number of cases It is almost invariably of the right side affecting chiefly the pulmonic valves It is nearly always of the chronic or sclerotic variety and it is often difficult to say whether the lesion has resulted from infection of the heart valves or represents an error in development In many instances the processes are combined infection being superimposed upon a structurally imperfect valve The majority of congenital cardiac lesions can be traced to defective growth

Pathology —In most cases several lesions are present so that a variety of combinations is possible and is indeed encountered To enumerate them would involve making a catalogue of cardiovascular curiosities and would serve no practical end The following clinical classification proposed by Maude Abbott is particularly useful for prognosis

I *The Group without Cyanosis* —There is no abnormal communication between the two circulations the anomaly itself is the seat of strain The lesions are mostly on the left side They include simple dextrocardia anomalies of the pericardium (defect or diverticulum) coarctation of the aorta (adult type), primary congenital hypertrophy sub aortic stenosis, aortic or mitral stenosis or atresia bicuspid aortic valve right or double aortic arch right subclavian artery arising from the descending aorta and left coronary artery arising from the pulmonary artery

II *The Group with Possible Transient or Terminal Cyanosis* (*Cyanose Tardive*) —An arterial venous shunt is present but there is no cyanosis unless circumstances arise which raise the pressure in the right side of the heart Then transient or terminal reversal of flow takes place, with venous blood entering the arterial stream Included in this group are patent ductus arteriosus, defect of the aortic septum defect of the auricular septum patent foramen ovale and defect of the ventricular septum

III *The Group with Cyanosis* —There is a permanent venous arterial shunt and venous blood in considerable quantity enters the systemic arterial circulation In this group are included pulmonic stenosis with or without septal defect, pulmonic atresia transposition of the great arterial trunks cor triloculare, persistent truncus arteriosus, and the tetralogy of Fallot, in which there is pulmonic stenosis defect of the ventricular septum dextroposition of the aorta and right ventricular hypertrophy

The commonest lesions encountered in the order of frequency are interauricular septal defect interventricular septal defect patent ductus arteriosus pulmonic stenosis anomalies of the semilunar cusps coarctation of the aorta (adult type), and transposition of the arterial trunks It is important to remember that in the great majority of cases several lesions are present The most frequent combinations are pulmonic stenosis with defective ventricular septum pulmonic stenosis with defective auricular septum the three defects associated or pulmonic stenosis and defective ventricular septum with patent ductus arteriosus Of 242 cases tabulated by Holt only 23 showed a single lesion

For purposes of description two main types of defect may be distinguished (1) anomalies of position (2) anomalies of structure

Anomalies of Position —Absence of the heart *acardia* is a rare monstrosity In *ectopia cordis* the ventral thoracic wall fails to unite in the midline and the heart may lie outside the chest cavity though enclosed by pericardium and covered by skin and subcutaneous tissue The heart may be situated in the cervical pectoral or abdominal regions Under these circumstances extra uterine life is rarely possible

Of some clinical interest are the instances of *dextrocardia* which may or may not be associated with transposition of the

per cent The leukocytes are increased but little, if at all The temperature tends to be subnormal The children are often under sized and backward in development Mental retardation may be an associated anomaly or an effect of the circulatory condition In infants feeding furnishes a difficult problem Attacks of syncope precordial pain and epileptiform convulsions are sometimes very distressing In some instances despite the presence of cyanosis and cardiac enlarge ment the patient may make no complaint of discomfort

Diagnosis —In the diagnosis of congenital heart disease two distinct problems are presented first a congenital must be dis tinguished from an acquired lesion second a precise anatomic differentiation of the va rious defects may be attempted The recog nition of a congenital lesion is of prognostic importance and is usually relatively easy The complexity of the numerous combina tions of defects and the variability of the physical signs make precise definition of the structural anomalies extremely difficult In the majority of cases only a probable anatomic diagnosis can be made

Cyanosis clubbed fingers a loud murmur (usually systolic) and cardiac hypertrophy are the chief diagnostic features Occurring in a young individual who has never had any of the manifestations of rheumatic in fection with a history of symptoms begin ing in infancy or early childhood they are of particular significance The cases without cyanosis seen in older children occasionally offer some difficulty in distinguishing con genital from acquired disease The intensity of the murmur the absence of left ventricu lar hypertrophy the persistent absence of symptoms and a lesion which gives no signs of progres ion favor the opinion that there is a congenital malformation In an emic children basal systolic murmurs may raise the question of the existence of a con genital lesion Such murmurs are softer than those due to congenital defects and are un accompanied by cardiac enlargement or cyanosis Subsequent examination when the general condition has improved serves to decide the issue

Murmurs are present in practically every case sometimes particularly in infants none is heard They are usually systolic in time and harsh in quality Though often audible over a wide area the point of maximum in tensity is either at the base or over the body of the heart very rarely at the apex. A systolic murmur at the base is most fre quently *due to pulmonic stenosis* less com monly to aortic stenosis When heard loudest over the body of the heart especially along the left sternal border it is some times indicative of a defect in the inter ventricular septum In view of the fact that pulmonic stenosis and patency of one of the cardiac septa are so often associated it is difficult to decide upon which lesion the murmur depends In pulmonic stenosis the second pulmonic sound is usually diminished in intensity A systolic thrill may or may not be present It is not of diagnostic impor tance Cardiac enlargement especially to the right is present in most cases

A *patent ductus arteriosus* is recognized by the presence of a long loud continuous murmur with systolic intensification best heard in the second or third left interspace It may be audible only during systole The second pulmonic sound as a rule is sharply accentuated As pointed out by François Franck the murmur is often heard loudly in the left side of the back over the area at which the aorta comes in contact with the chest wall at the level of the third and fourth dorsal spines The louder the mur mur the smaller is apt to be the caliber of the ductus and vice versa When the patent vessel is wide the systolic blood pressure tends to be elevated and the diastolic low so that the pulse pressure is increased Fluoroscopic examination may show an ab normal bulging of the left upper border of the heart shadow due to dilatation of the pulmonary artery The electrocardiogram usually shows no axis deviation

In *coarctation of the aorta* hypertension develops in the brachial vessels and this is associated with feeble or absent femoral pulsation The blood pressure in the legs is lower than in the arms and often is difficult to obtain Signs of enlargement of the left ventricle are present in about half the cases A systolic murmur at the aortic area is fre quent Sometimes attention is first directed to the condition by dilated strongly pulsat ing dorsal scapular or intercostal arteries which as anastomotic channels convey

with arduous activity The average duration of life is about thirty five years

ANOMALIES OF THE VALVE CUSPS are not uncommon and usually involve the semilunar segments at the arterial openings The segments may be increased or decreased in number Supernumerary segments, if present are apt to be small and are more frequently seen at the pulmonary opening than at the aortic The bicuspid condition is present more often at the aortic orifice Observations of Thomas Lewis suggest that the bicuspid aortic valve is of more than casual interest and importance He believes that valves so formed antenatally are malformations there being no evidence that they result from fetal endocarditis Among males reaching adult life and possessing congenitally bicuspid aortic valves 23 per cent at least die of active endocarditis In an unselected series of thirty one cases of subacute bacterial endocarditis 26 per cent presented bicuspid aortic valves and among those of the thirty one cases in which the aortic valve was the seat of vegetations 40 per cent showed the bicuspid malformation Thus a congenitally bicuspid aortic valve often appears to determine the localization of subsequent bacterial endocarditis owing to a susceptibility to infection induced by the congenital malformation Why this happens is unknown

Anomalies of the AURICULOVENTRICULAR VALVES are rarely seen

Less than 50 cases of CONGENITAL HEART BLOCK, with complete or partial auriculoventricular dissociation confirmed by graphic records have been reported It is probable that in all of these a congenital malformation of the conduction system was responsible for the cardiac irregularity although careful histologic study of the heart was made in only a few instances

Anomalies in the origin of the CORONARY ARTERIES are rare They may cause cardiac hypertrophy and inverted T waves in the electrocardiogram

Symptoms and Signs —The evidences of congenital heart disease are usually apparent soon after birth but may not manifest themselves until later in life The onset of symptoms may be definitely related to a contributory cause In a case observed several years ago cyanosis first appeared at the age of two on the day following tonsillectomy Up to that time there had been no suspicion of a cardiac defect The child died at the age of six Occasionally there are no symptoms until after puberty

Cyanosis is the most striking objective symptom and is responsible for the employment of the term *morbus caeruleus* by the earlier writers The mother often refers to the fact that the child was a 'blue baby at birth In the severer cases cyanosis is almost invariably present but taking into account all varieties of defect it is observed in about half of the total number It is conspicuous particularly in the lips cheeks nose ears fingertips and toes The patient may be of a livid color as though stained with the juice of blueberries In 1861 Knapp called attention to the dilatation tortuosity and deep violet color of the vessels in the fundus of the eye If congestion is marked retinal hemorrhages may occur The factors concerned in the production of cyanosis have not been conclusively established It is presumably due in part according to Lundsgaard and van Slyke to the passage of unaerated blood directly from the right heart to the arterial system in part to deficient oxygenation of the blood in the lungs due to disturbances in the pulmonary circulation If heart failure is present and the circulation is slowed increased oxygen consumption by the tissues per unit of blood flow may enter into the group of causes concerned

Clubbing of the terminal phalanges of the fingers and toes usually accompanies cyanosis The changes affect chiefly the soft tissues very rarely the bones The occurrence of dyspnea is determined by the character and severity of the lesions If there is no cyanosis there may be no shortness of breath The degree of respiratory discomfort varies in large measure with the amount of oxygen unsaturation In the later stages when cardiac failure dominates the picture dyspnea is extreme and is accompanied by other symptoms of myocardial insufficiency Hemoptysis and epistaxis are not infrequent

In the cases showing marked cyanosis polycythemia is present The red blood cells may vary from 7 000 000 to 12 000 000 and there is a corresponding increase in hemoglobin This I have observed as high as 160

Medical treatment is largely symptomatic Infections particularly of the respiratory tract should be prevented as far as possible The amount of physical activity which is permitted must be determined according to the functional capacity in each case Congestive heart failure if present is managed in the usual manner

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RHEUMATIC HEART DISEASE

Definition —Heart disease is one of the manifestations of rheumatic fever It is not a complication as related lesions may be present elsewhere Although the heart may be involved simultaneously with such other manifestations of rheumatic fever as polyarthritis chorea and subcutaneous nodules it is frequently the first and only structure to be implicated The various inflammatory changes in the heart which arise in rheumatic fever together with the valvular deformities and other scars that remain constitute rheumatic heart disease

Classification —Rheumatic heart disease may be active or inactive or both The former implies that rheumatic infection is present in one or all of the structures of the heart. Inactive rheumatic heart disease means that infection has ceased but that healed lesions remain usually valvular deformities the result of previous inflammation

Another clinical grouping (Swift) includes four types namely, fulminating recurrent active chronic active and chronic inactive. The first type which usually terminates fatally during the initial attack of rheumatic fever is rare and almost always occurs in children The recurrent active type is characterized by intervening intervals of quiescence or inactivity the chronic active type by signs of inflammation persisting over periods of months or years The chronic inactive type exists for years with no signs or symptoms of rheumatic infection and presents healed structural lesions

Incidence —Rheumatic heart disease is the commonest form of heart disease occurring in childhood It is responsible for fully 90 per cent of defective hearts in children It is the second most prevalent form of heart disease in adults and accounts for about 30 per cent of the crippled hearts in that age period About 90 per cent of rheumatic heart disease occurs before fifty years of age and more than half before thirty

Rheumatic heart disease usually exists alone In a small number of cases it is associated with other forms of heart disease such as that of syphilis or with congenital malformations Not infrequently however rheumatic heart disease is accompanied by hypertension especially in older individuals with mitral stenosis

Sex —Rheumatic heart disease is equally distributed between the sexes although it is sometimes said that girls are more often affected

Race —The part played by racial susceptibility in rheumatic fever and rheumatic heart disease has not been fully established largely because methods for determining race prevalence are not satisfactory

Climate —That rheumatic heart disease has different geographical distributions apparently depending on climatic influences is recognized but no single satisfactory explanation has been offered thus far It is agreed that it is commonest in northern latitudes particularly in the northeastern part of the United States and in the British Isles

Age —Rheumatic heart disease is predominantly one of childhood and early adult

blood to the lower aorta through the internal mammary and superficial epigastric vessels In x ray films the borders of the ribs may show erosion due to the repeated pulsations of the enlarged intercostal arteries against the adjacent bone

An abnormal position of the heart as in *dextrocardia* causes the apex beat to appear in an unusual location and the cardiac out line as mapped out by percussion does not occupy its customary place Confirmatory evidence is afforded by x ray examination

Transposition of the great vessels is un common and is incompatible with survival for more than a few days unless there is an associated septal defect Cyanosis is an al most invariable sign Murmurs and thrills depend upon the presence of other anomalies Roentgenologic examination may show little except cardiac enlargement

Electrocardiographic examination is of particular diagnostic aid in dextrocardia In this condition the cardiac axis is rotated so that in Lead I the usual waves are in verted Lead II corresponds to the usual Lead III and Lead III to the usual Lead II In other forms of congenital defect vari ous types of change have been recorded The excursions are often wide and there may be right or less often left axis deviation In congenital heart block electrocardio graphic records clearly demonstrate the disturbed cardiac mechanism

Course and Prognosis—These vary with the type of lesion Some forms of malforma tion do not permit of survival for more than a few days weeks or months In cases with no shunt between the arterial and venous systems and hence without cyanosis life may be normal with respect to both ac tivity and duration Patients with minor septal defects uncomplicated patent ductus arteriosus dextrocardia or coarctation of the aorta of moderate degree fall into this cate gory The intensity of the murmurs is of no prognostic significance

When cyanosis is present the outlook is more serious for anoxemia places an added burden upon a heart already laboring under a mechanical handicap The degree of con gestive heart failure which develops deter mines the issue unless life is terminated by an intercurrent complication Occasionally a patient with pulmonic stenosis may survive to a mature age provided this lesion is ac companied by an adequate compensatory anomaly, such as a patent interventricular septum or an open ductus arteriosus

Of 225 cases collected by Holt 60 per cent died before the end of the fifth year and nearly half of these during the first two months 16 per cent lived over sixteen years and 8 per cent over thirty years Patients with congenital cardiac disease are particu larly susceptible to infection superimposed upon the lesions, and a number die of bac terial endocarditis Any acute malady may prove fatal When coarctation of the aorta is present the end sometimes comes as the result of spontaneous rupture of this vessel or of cerebral hemorrhage In the group with cyanosis sudden death is not infrequent some die of pulmonary tuberculosis but con gestive heart failure is the commonest terminal event

Treatment—A notable advance in the surgical therapy of congenital cardiac dis ease was made in 1939 when Gross reported the first successful ligation of a patent duc tus arteriosus Since then, a sufficiently large series of cases has been operated upon in various clinics to demonstrate the safety and efficacy of the procedure Indications for operation are malnutrition retardation of growth or evidence of cardiac insuffi ciency The hope has been expressed that ligation might lessen the likelihood of the subsequent development of bacterial en darteritis at the site of the anomaly but data in support of prophylactic closure are not yet available Certainly in many per sons an open ductus is compatible with a long and active life

After infection has occurred and particu larly if this is of relatively short duration ligation may cure the resulting sepsis The most common invading organism is *Strep tococcus viridans* Chemotherapy with one of the drugs of the sulfonamide group or with penicillin sometimes appears to aid in sterilizing the blood stream In the presence of an associated congenital cardiac anomaly of valvular involvement or of peripheral embolization a favorable outcome is doubt ful

A technic for the surgical therapy of other congenital defects has not yet been devel oped

one in 40 per cent of cases In about half of all patients there are no evidences of infection after thirty years of age

Symptomatology —The signs and symptoms of rheumatic fever are discussed in detail in the chapter on Rheumatic Fever (p 435)

The clinical signs and symptoms of *carditis* are caused as a rule by inflammation of the myocardium and valves less commonly of the pericardium Acute rheumatic myocarditis may be recognized by tachycardia fever and leukocytosis rapid sedimentation rate gallop rhythm changes in quality and intensity of the first heart sound blowing systolic murmur at the apex and enlargement of the heart due to dilatation Sometimes irregularities in rhythm including premature contractions or auricular fibrillation make their appearance Auricular fibrillation always indicates a severe degree of myocardial damage and invariably leads to cardiac insufficiency However the latter may occur in the presence of sinus rhythm Complete heart block is rare but a partial degree of block especially first stage block is common

It has been shown that a mid diastolic rumbling sound or murmur at the apex previously considered indicative of mitral stenosis and quite commonly heard in children during severe rheumatic infection may be caused by myocardial dilatation alone. The blowing systolic murmur so frequently heard at the apex may also be the result of cardiac dilatation although dysfunction of an inflamed mitral valve may play a role The most important aids in the recognition of myocarditis are the electrocardiographic changes These are found in the majority of patients As a rule frequent tracings are necessary because the abnormalities are often transient Among the more common deviations are prolongation of the P R interval denoting increased auriculo ventricular conduction (partial block) abnormalities in the QRS complexes and S T and T waves

Active valvulitis especially of the mitral less frequently of the aortic valves invariably accompanies the active myocarditis of rheumatic heart disease It is perhaps the commonest lesion of the heart in rheumatic fever Whether it is present however is largely a matter of conjecture The active inflammatory changes in the valve itself and the verrucae on its margins are probably not sufficient to produce deformity of the orifice but may cause dysfunction of the valve by improper closure of the leaflets thereby producing murmurs These changes together with inflammation of the ring portion of the valves and the concomitant myocarditis may cause dilatation of the valve rings and resultant incompetency This is most common at the mitral and somewhat less frequent at the aortic orifice Enlargement of the heart may be detectable in such instances but an early high pitched diastolic murmur over the base or along the left border of the sternum resembling that of aortic insufficiency may be audible as well as a blowing systolic murmur localized at the apex. Both murmurs may disappear after the inflammatory changes have subsided but may reappear when valvular deformities develop

In from 5 to 25 per cent of all cases acute valvulitis and myocarditis may be part of a *pancarditis* in which the pericardium is likewise involved This occurs in children who are usually severely ill with rheumatic fever about 1 per cent of them suffer a rapidly fatal course In all children with rheumatic pericarditis however the prognosis is bad both immediate and ultimate In older patients pericarditis may in an occasional case occur without involvement of the valves or of the myocardium or with only slight inflammation of one or the other of those structures Years later examination of such patients may reveal no evidence of organic heart disease

Contrary to belief *pain* is not a common symptom in rheumatic pericarditis The *pathognomonic sign* is the to and fro friction rub a superficial scratchy sound heard over the precordium This rub may last for hours or persist for days or weeks even in the presence of relatively large effusions In the latter circumstances it may be audible only over the basal regions With the increase of fluid in the sac the area of cardiac dulness especially to the right but also to the left may be increased the heart sounds may grow fainter and a paradoxical pulse may appear In addition *Ewart s sign* may be elicited It consists of dulness bronchial breathing and bronchophony in the left infrascapular area Occasionally children with

life and usually runs its course within the first four decades The onset is oftenest between the ages of five and ten with the maximum at eight years On the other hand, it may begin at any age even as late as the sixth decade About 70 per cent of individuals afflicted with this disease are known to have acquired it before fifteen years of age The period of economic usefulness of a rheumatic cardiac patient is on the average not more than eleven years after the initial infection

Etiology and Morbid Anatomy—The cause of rheumatic heart disease is rheumatic fever However in from 20 to 30 per cent of patients with rheumatic heart disease no antecedent history of rheumatic fever is obtainable Therefore the criteria for the diagnosis of rheumatic fever as a cause of heart disease have been made rather broad and include (1) a history of polyarthritis chorea muscle or joint pains or subcutaneous nodules and evidences of a structural lesion of the heart, (2) evidence of a structural lesion plus a history of periods of recurrent fever and cardiac insufficiency' A discussion of the etiology of rheumatic fever including its bacteriologic and immunologic aspects is given elsewhere (p 437) This also holds for the pathologic aspects which are covered under Rheumatic Fever (p 435) and Chronic Valvular Diseases (p 1076)

Development and Mode of Onset—Infection in the form of polyarthritis muscle and joint pains chorea and carditis is the characteristic mode of onset in more than 80 per cent of patients who acquire rheumatic fever before the age of ten years After the age of forty somewhat more than 20 per cent exhibit this form of the disease Before the age of ten valvular lesions alone are the first manifestations in about 15 per cent of cases after forty in almost 80 per cent In childhood the onset of rheumatic heart disease is characterized by polyarthritis in about 50 per cent of all cases and by carditis and chorea in about 33 per cent In young adults the onset is marked mainly by polyarthritis and in older individuals by the appearance of valvular lesions alone that is to say without a history or signs of infection

Chorea, the muscle and joint pains occur as initial manifestations almost exclusively before puberty and practically never after twenty-one years of age Both are associated with a milder form of rheumatic fever and the incidence of carditis is low

It is now conceded that rheumatic fever is a chronic infection Recurrent signs of an active inflammation are commonly seen in children and one or more recrudescences occur in about 75 per cent The largest number of recurrences occur between five and fifteen years although no age is exempt Of interest is the observation that the younger patient is likely to present several different manifestations of infection during the recurrences whereas the adult is apt to show the same manifestation repeatedly and usually it is the same as that which characterized the initial attack

The earlier the age at which rheumatic fever and rheumatic heart disease are acquired the more common are the recurrences of active infection It has been shown that recurrent infections begin to decrease at puberty suggesting that some form of resistance develops Other observers believe that regardless of age recurrences of rheumatic fever are less likely to occur five or more years after the initial episode because of the development of immune processes This five year period frequently coincides with the beginning of puberty The studies of Cohn and Lingg ' tend to support the opinion that it is puberty, and not necessarily the first five years after the initial infection that influences the frequency of recurrent activity They further state that There can be little doubt that knowledge of this diminishing susceptibility to rheumatic infection at puberty is of value in judging the effect of therapeutic measures on the subsequent course of the disease and that age therefore is an important factor in estimating the effect of treatment

Type of Infection—When rheumatic fever begins in childhood carditis is the commonest but rarely the only type of infection The mixed type especially the combination of carditis and polyarthritis is commonest among children but decreases in the older age periods During adolescence and early maturity carditis is seen more frequently as a single manifestation At all ages polyarthritis is the most frequent single sign Between fifteen and thirty years it is the only

sidered characteristic of valvular disease It has been reported by others that in groups of patients followed for still longer periods of time 20 to 37 per cent recover completely Since it is known that the later in life a patient suffers a first attack the better the chances for recovery it is probable that these latter groups included many older patients About one half of those who are afflicted between the ages of twenty and forty years do not develop rheumatic heart disease After the age of forty the percentage is higher

Inactive Rheumatic Heart Disease —This form of heart disease is symptomless unless complications supervene such as congestive heart failure auricular fibrillation or flutter embolism or subacute bacterial endocarditis The period during which a patient remains symptom free averages ten to twelve years This may be followed by signs of cardiac insufficiency and subsequently by those of congestive heart failure

The mitral valve is involved in almost every patient with rheumatic heart disease An occasional patient usually a young adult may show involvement of the aortic valve alone invariably with insufficiency More rarely isolated aortic stenosis is recognized in patients about fifty years of age Mitral stenosis usually combined with insufficiency is the commonest lesion of rheumatic heart disease occurring in approximately two thirds of all patients but mitral insufficiency alone is uncommon especially in adults It is found more frequently in children and oftenest in the course of the five years following the first attack of rheumatic fever

Clinically combined mitral and aortic valvular lesions occur in approximately one third of all cases of rheumatic heart disease Mitral or aortic deformity combined with tricuspid lesions occurs in a smaller group about 10 per cent The pulmonic valve is rarely affected On the other hand involvement of the tricuspid and pulmonic valves as determined by necropsy is more common The degree of deformity which occurs in these circumstances is usually mild and is not sufficient to cause appreciable alterations in the function of the valves Hence it is not clinically recognizable

Patients afflicted with rheumatic valvulitis in the first decade of life and especially in those with severe infections or recurrent periods of activity are apt to develop more than one valvular deformity This explains why multiple valvular lesions are so frequently found in adolescents Among individuals infected later especially among those who survive the age of thirty years mitral stenosis is commonly found as an isolated lesion

Diagnosis —The determination of inactive rheumatic heart disease in the absence of symptoms depends largely on detection of the signs produced by the several valve deformities This aspect is more fully considered in the chapter on Chronic Valvular Disease (p 1076)

Complications —Although complications may occur in both the active and inactive forms of rheumatic heart disease they are distinctly more common in the latter group Probably the most frequent is *cardiac insufficiency* as revealed by increased fatigue and dyspnea which constitutes the first signs of diminution in functional capacity of the heart Such symptoms are sooner or later experienced by nearly all rheumatic cardiac patients although the interval between the onset of rheumatic fever and signs of cardiac insufficiency is about ten years Within three or four years after these symptoms appear for the first time about 50 per cent of the patients die in spite of treatment

When symptoms of cardiac insufficiency are so easily induced that patients become distressed on slight exertion or even while at rest *heart failure* may then be said to exist As a general rule patients begin to show signs of heart failure about two years after symptoms of cardiac insufficiency appear About 80 per cent of rheumatic cardiac patients suffer at least one attack of heart failure The signs and symptoms include dyspnea on effort or paroxysmal dyspnea or both orthopnea distended neck veins tenderness of the liver pulmonary congestion and edema hydrothorax and sacral and leg edema When the patient shows signs of heart failure his life expectancy is brief—from three to five years

A common complication of rheumatic heart disease is *embolism* The source of emboli is usually a thrombus in one of the auricles or auricular appendages Emboli may be carried to almost any part supplied

large pericardial effusions show signs of respiratory distress such as marked dyspnea and orthopnea

Fluoroscopy may show an enlarged cardiac silhouette of pyramidal shape if the effusion is moderate and water bottle in outline if marked The cardiac pulsations are diminished or absent A characteristic electrocardiographic pattern is found in many cases consisting of elevation of the S T segments in the standard leads as well as in the chest leads In the former, elevation may be especially marked in lead 2 or in leads 1 and 2 combined These abnormalities are usually found early notably during the stage of fibrinous exudation and are transient disappearing in a few days If marked effusion occurs these changes are usually not seen but there may be lowering of the voltage of the QRS complexes and the T waves sometimes with shallow inversion of the latter

In children *congestive heart failure* may be precipitated by carditis even during the initial attack of rheumatic fever In fact at any time during childhood or adolescence its presence in a patient with rheumatic heart disease should be regarded as evidence of active rheumatic infection The clinical manifestations include dyspnea orthopnea cough distended neck veins moist basal rales enlarged and tender liver and sacral or leg edema or both It indicates a bad prognosis and is the commonest cause of death in all forms of rheumatic heart disease

Subsequent Course—In children it is unusual for all signs of carditis to subside within a few weeks of the onset of the initial phase of rheumatic fever The inflammatory lesions are more often of several or many months duration and in some may persist for years In others the process seems never to become quiescent these are the chronically active rheumatic cardiac patients The chronicity of rheumatic fever although frequently emphasized is not sufficiently recognized

Disappearance of the clinical signs of active carditis does not necessarily mean that the inflammatory process has become inactive Other evidence of its presence may persist for periods ranging from weeks to months and occasionally years Helpful laboratory findings include electrocardiographic abnormalities especially prolonged A V conduction time and elevated sedimentation rates It is important to recognize this phase of active rheumatic heart disease in order to prevent further damage to the heart by ill advised premature physical activities

Rheumatic fever in childhood is a chronic or recurring disease It is unusual for a child to have only one attack of carditis Recurrent active rheumatic heart disease is usually met with during the five or six years following the initial attack It is important to recognize recurrent periods of activity because progressive damage to the heart may occur during these periods and not infrequently heart failure and death if adequate rest and similar measures are not enforced Active infection is responsible for most deaths in children with rheumatic heart disease Clinical recognition of infection is sometimes difficult but use of the laboratory tests mentioned may lead to a correct diagnosis

Development of Inactive Rheumatic Heart Disease—The conception that the heart is always involved to some degree in rheumatic fever is widely entertained but that it is possible for individuals who have had carditis to have normal hearts years later is not fully recognized Undoubtedly such patients may have had enlargement of the heart together with systolic and diastolic murmurs during their initial attacks of rheumatic fever but they probably did not have valvulitis or if they did at most a minimal degree It is even probable that some who have had appreciable degrees of valvulitis may develop scarring without significant valvular deformity it persists however although the characteristic murmurs have disappeared

Valvular deformities of sufficient degree to produce stenosis at the orifice or insufficiency of the valve develop as a rule six months to two years or even longer after the onset of infection of the valves However not all individuals who suffer an attack of rheumatic fever develop permanent heart disease Over an observation period of ten years about 8 per cent of children reveal regression or even complete disappearance of those physical signs which are con

two thirds of them die during this period Nearly one third of the patients in whom the onset is in childhood do not survive beyond childhood and about another one third do not survive adolescence However it appears to be true that children who survive adolescence have a good chance of reaching maturity The main factor here as previously discussed is the influence of puberty

In about 80 per cent of all cases the cause of death in children with rheumatic heart disease is rheumatic fever and carditis with or without congestive heart failure Unknown causes and causes other than heart disease account for an additional 10 per cent

In adults death is due to heart disease in about 75 per cent of cases the largest number dying of congestive heart failure and about 6 per cent of bacterial endocarditis About 10 per cent of deaths are the result of thrombosis or infarction and the remaining are caused by conditions other than heart disease

Prophylaxis—The association of rheumatic fever with hemolytic streptococcal infections led to the prophylactic use of sulfanilamide After seven years of investigation by many different observers it has been established that this drug has a beneficial effect in preventing recurrent attacks of rheumatic fever During this time several hundred children and young adults received sulfanilamide prophylactically and recrudescences occurred in less than 1 per cent

Adequate protection seems to be afforded by small doses such as 1 to 1.5 Gm daily even in older patients At present there is no basis for determining the minimal blood level which will give protection against invasion of the streptococcus Toxic reactions such as transient rashes fever gastro intestinal disturbances and slight leukopenia rarely occur with such doses Patients who tolerate the drug for two weeks are apt to remain symptom free thereafter Those who develop untoward symptoms should discontinue the drug for several weeks They may resume it in smaller doses gradually increasing the dose over a period of weeks to the desired level Complete white blood counts and hemoglobin determinations are the only routine measures that need be performed particularly during the early weeks of its administration Since most of the recurrent attacks of rheumatic fever occur within five years of the initial attack prophylactic sulfanilamide therapy should be continued over a period of at least five years

Because it is agreed that one of the best preventive measures in the care of the patient with rheumatic heart disease is to keep him free from hemolytic streptococcal infections it is often necessary to remove contributing foci such as diseased tonsils and adenoids and infected sinuses Preceding such operative procedures sulfanilamide should be administered to prevent the development of subacute bacterial endocarditis

Treatment—The care of the patient with rheumatic fever and its cardiac manifestations is described in detail in the chapter on Rheumatic Fever (p 435–450) The treatment of the *recurrent active* or *chronic active forms* of rheumatic heart disease is essentially the same as that of the initial attack of carditis One of the complications in active rheumatic heart disease is congestive heart failure Its treatment is not agreed upon by all authorities Some employ digitalis others do not or even regard it as hazardous The latter group administers mercurial diuretics instead Experience with digitalis on the whole has been satisfactory although there are some patients especially those with fulminating infections who do not respond because of widespread myocardial inflammation It should be given by mouth and with caution especially in children One should be on the alert for evidences of therapeutic effect and for signs of early toxicity Frequent electrocardiographic records should be made

Treatment of the *inactive phase* of rheumatic heart disease is directed mainly toward those complications which may arise Cardiac insufficiency can usually be corrected by digitalis Auricular fibrillation may sometimes be abolished by quinidine particularly when this arrhythmia first makes its appearance and there are no contraindications to its use The majority of such patients cannot be maintained at regular sinus rhythm by the daily use of quinidine for longer than six to eight months Auricular fibrillation invariably returns In such

by the systemic or pulmonary circulations when they arise in the left side of the heart however they are apt to lodge in the brain, spleen kidneys or extremities and in the lungs when they arise in the right side Pulmonary infarction is probably the commonest postembolic manifestation of rheumatic heart disease and is particularly common in patients with mitral stenosis attended by auricular fibrillation It occurs oftenest in the lower lobe of the right lung and is frequently associated with pleuritis Involvement of the pleura is the cause of the sudden sharp pain in the side experienced by many patients at the time that infarction of the lung takes place Hemoptysis is a fairly frequent occurrence in patients with mitral stenosis Cerebral emboli with resultant paralyses of various degrees and locations are common occasionally they cause almost immediate death Embolic occlusions of vessels in the extremities usually the lower if complete result in gangrene irrespective of treatment. Many cause only partial occlusion or resolve so that the circulation returns and restoration follows Emboli to the kidneys although they are usually painful may be silent Subsequent infarction gives rise to hematuria

Arrhythmia —The commonest irregularity of rhythm complicating rheumatic heart disease is caused by auricular fibrillation and occurs in about 50 per cent of rheumatic cardiac patients The longer rheumatic heart disease lasts the more likely is auricular fibrillation to occur *It is most commonly* observed in the fourth decade of life

Auricular fibrillation occasionally occurs in childhood and in the adolescent period as an acute complication of the active phase of rheumatic heart disease It contributes also to the fatalities occurring during the *initial five year* period of infection It indicates severe infection of the myocardium and the prognosis is correspondingly bad Patients with rheumatic heart disease and auricular fibrillation who die of congestive heart *failure before* the age of forty years invariably present evidences of active rheumatic infection at necropsy and sometimes clinically

The highest incidence of auricular fibrillation is in patients with mitral stenosis It is less frequent in those with combined mitral and aortic valvular deformities That it is present in the majority of patients with mitral and tricuspid lesions is a fact of some importance

In an appreciable percentage of rheumatic cardiac patients especially those with mitral stenosis, embolism occurs following intra auricular thrombosis Embolism of course may cause infarction of any organ with so called terminal arteries or in any organ when the arteries are too small to permit the passage of emboli

The view that auricular fibrillation is a *late phase in rheumatic heart disease* appears to be supported by statistical analyses These seem to show that about 75 per cent of rheumatic cardiac patients who develop auricular fibrillation die within three years of its onset

Bacterial Endocarditis —About 6 per cent of children with rheumatic heart disease die of acute or subacute bacterial endocarditis Among adult rheumatic cardiac patients the incidence varies between 6 and 10 per cent the majority succumbing to the subacute type of infection As a rule subacute bacterial endocarditis in both children and adults involves valves which do not present severe degrees of stenosis and hence it is commonly seen in uncomplicated mitral or aortic insufficiency or both It practically never happens in association with auricular fibrillation because subacute bacterial endocarditis usually occurs in the second and third decades of life during which periods *auricular fibrillation is almost* never present However in about one half of the cases bacterial invasion takes place while rheumatic infection is still active in the heart. This may not be proved clinically but is readily demonstrated at necropsy

Prognosis —Life expectancy in rheumatic heart disease is apt to be short About 50 per cent live nine years about 25 per cent longer than seventeen years and about 10 per cent longer than thirty years after the onset The *mean* duration from onset to death is about thirteen years and there is no essential difference between the sexes The *mean* age at death is given as thirty three years

The highest mortality rate in children occurs during a period of from three to five years after the initial attack of carditis *about*

two-thirds of them die during this period Nearly one-third of the patients in whom the onset is in childhood do not survive beyond childhood and about another one third do not survive adolescence However it appears to be true that children who survive adolescence have a good chance of reaching maturity The main factor here as previously discussed is the influence of puberty

In about 80 per cent of all cases the cause of death in children with rheumatic heart disease is rheumatic fever and carditis with or without congestive heart failure Unknown causes and causes other than heart disease account for an additional 10 per cent.

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circumstances digitalis is the drug of choice It is also indicated if the arrhythmia is complicated by congestive heart failure When signs of failure become so severe that digitalis alone cannot control them, mercurial diuretics administered intravenously or intramuscularly should be tried If paroxysmal dyspnea with or without pulmonary edema appears the intravenous administration of aminophylline is frequently effective Phlebotomy either by actual venesection or by the application to the extremities of blood pressure cuffs inflated to a pressure a little higher than the patient's diastolic level sometimes gives dramatic relief

The treatment of choice in *embolic occlusion* of the arteries of the extremities is papaverine in large doses (0 1 to 0 2 Gm) given intravenously Paravertebral sympathetic block is also useful to reduce the vasoconstriction of collateral as well as of main branches Some patients respond to these or similar forms of therapy and the affected extremities return to normal Others develop gangrene and amputation becomes necessary Some believe that embolectomy is indicated in all cases but in view of the large number of recoveries with more conservative measures this seems of doubtful utility except in selected cases Pulmonary infarction also responds to papaverine but the pleuritic pain may require codeine Embolism of the spleen or kidneys causes sudden sharp pain which is best treated by codeine alone Mesenteric embolism is apt to result in gangrene of a part of the intestine and is always serious Although the administration of papaverine intravenously is indicated restoration of the ischemic gut is rare and surgical intervention is necessary Emboli to the brain occur not uncommonly and depending on their size and location various degrees of paralysis take place or occasionally, death Complete recovery sometimes occurs

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ENDOCARDITIS

Definition—Endocarditis is an inflammation of the tissue lining the cavity of the heart particularly the tissue of the valves The simplest classification of the different types is as follows

1 Nonbacterial (*simple*)
    (*a*) Acute nonrheumatic
    (*b*) Acute rheumatic
2 Bacterial (*myocotic*)
    (*a*) Acute
    (*b*) Subacute

Syphilitic involvement of the endocardium is not considered in this classification since this disease is not primarily of the endocardium

Malignant endocarditis includes those forms of the acute bacterial type which are rapidly fatal In all types the inflammatory foci may ulcerate Since the lesions on the valves except for the simple erosions are spoken of as vegetations the terms *ulcerative* and *vegetative* are not distinctive The vegetations of the nonbacterial variety are called *verrucous* when they represent organized tissue reactions The initial erosion of the valve with its deposition of clot has been called *thrombo endocarditis*

Etiology—1 (*a*) There are cases of acute endocarditis in which no history of acute rheumatic fever can be obtained and in

which at autopsy the lesions usually regarded as typifying rheumatic fever are not found This type of nonrheumatic endocarditis is also nonbacterial because cultures from the valves and microscopic inspection of the valves themselves furnish no evidence of the presence of bacteria This type has been fully described by Libman and Sacks In a series of 44 cases studied by the author such cases occurred five times The etiology in this group is now regarded as associated with disseminated lupus erythematosus since the cutaneous manifestations of the latter disease are frequently though not invariably present. It has been suggested (Gross) that the two groups of cases previously designated as disseminated lupus erythematosus and atypical verrucous endocarditis respectively should be put in a single category of Libman Sacks disease'

The analysis of Gross and associates clarifies the situations in which thrombotic nonbacterial vegetations may occur

(b) The etiology of acute rheumatic endocarditis is discussed in detail in the chapter on Rheumatic Fever (p 435)

2. The etiology of bacterial endocarditis is involved in the double factor of preceding damage to the endocardium with subsequent bacterial implantation on the damaged area When chronicity occurs in this form of endocarditis it is due to the lack of virulence of the causative bacteria

Morbid Anatomy —Erosions are the first lesions to occur and may become infected at once or be organized into verrucous vegetations which may either form scar tissue or themselves be later infected Just how the rims of the valves become eroded is uncertain but the process is apparently non specific because the appearance at autopsy is the same whatever the disease of which the valvular erosion was a complication

The fact that erosion occurs in the absence of demonstrable infection (as in protracted systemic disease) seems to point to a noninfectious origin Whether the agency producing the injury acts upon the surface of the valves or beneath the surface by way of the capillaries is unknown but no connection between the lesion and the underlying blood supply can be shown microscopically The final amount of vegetation and scar tissue depends upon the degree of initial injury and the number and severity of recurring injuries At autopsy it is common to find fresh erosions engrafted on old verrucous vegetations In rheumatic fever such recurrences are apt to be frequent and the consequent dense scarring and contraction destroy valve function Both the erosion and the verrucous vegetation are susceptible to bacterial implantation It is important to regard bacterial infection as a secondary phenomenon which may take place either during the original disease which caused the erosion or later in life. Thus during severe pneumonia the erosions may be immediately infected by the pneumococcus in the blood stream and produce an acute bacterial endocarditis or this immediate invasion may not take place and a streptococcus may later infect the tissue during an attack of tonsillitis

Simple erosions the earliest lesions on the valves consist macroscopically of very small swollen areas on the rim of the valve covered with a small delicate blood clot. Smears taken from these lesions contain fibrin and red blood cells but no bacteria Microscopically the lesion appears as simple loss of substance on the edge of the valve with deposit of eosinophilic material and red blood cells

Verrucous Vegetations —Macroscopically verrucous vegetations are firm white nodular swellings along the rim of the valve which vary in size from 0.5 to 2 mm Microscopically they are composed of homogeneous pink staining fibrinoid material surrounded by a zone of round cell infiltration These vegetations do not contain bacteria In the early lesions of rheumatic endocarditis underlying proliferations resembling Aschoff bodies are frequent In their later stages the nodular appearance is lost in the diffuse thickening and puckering of the valve Fresh erosions may develop on these vegetations

For statistics concerning the anatomic distribution of rheumatic valvular lesions the reader is referred to the exhaustive studies of Thayer which are supported by the evidence of autopsies The simultaneous involvement of the aortic and mitral valves is the most common condition The tricuspid valve was involved in 41 66 per cent of 24 autopsies in the series studied by Thayer

In the early stages of rheumatic endocarditis, fresh areas of infiltration containing characteristic Aschoff lesions may be found also in the wall of the left auricle

In patients who survive the *rheumatic* fever of childhood, and who die in middle age it is not unusual to find typical Aschoff bodies but intercurrent bacterial rather than rheumatic processes may be responsible for the final undermining of cardiac structure This fact, together with the fact that the occurrence of early mild rheumatic fever is easily overlooked or forgotten make the position of so called 'nonbacterial nonrheumatic endocarditis insecure in any classification

Bacterial vegetations differ sharply from the verrucous In gross appearance they measure from 1 to 15 mm in diameter When washed free from their enmeshed blood they are spongelike or coral like in structure and show formations obviously guided by the currents about them They are gray in color but the firmly attached clot gives them a reddish brown appearance They are friable and crush easily between the fingers They are composed entirely of fibrin and bacteria At their bases there is active organization of the tissues of the valve There may be evidence in the neighboring valve tissue of old verrucous vegetations and fresh erosions may be seen elsewhere on the valve On the apparently uninvolved endocardial surface in the neighborhood of the vegetation, one may see microscopically superficial bacterial growth without underlying reaction in the tissues Mural endocarditis and softening and breaking of the chordae tendineae are comparatively frequent in all forms of bacterial endocarditis

Since the vegetation is affected by the character of the disease producing the preexisting or concomitant damage viz rheumatic fever pneumonia syphilis influenza sepsis the distribution of valvular lesions in bacterial endocarditis varies with the type under consideration pneumococcal endocarditis usually comes with lobar pneumonia occurs most frequently in later life and perhaps on account of this latter fact is found usually affecting the aortic valve The gonococcal infections are also most frequently of the aortic valve although the disease occurs at an earlier age In the streptococcal group the distribution of valvular injuries follows more closely the distribution in rheumatic endocarditis

RALPH A KINSELLA

NONBACTERIAL ENDOCARDITIS

Simple erosions are noticed at autopsy in many conditions such as chronic vascular disease and carcinoma in which a long period of debility preceded death This type of endocarditis is not diagnosed during life. Such erosions may also occur simultaneously with verrucous vegetations There is little or no clinical evidence of the existence of this type of endocarditis and frequently when the clinician assumes because of a systolic murmur noted during a terminal or febrile process that such endocarditis exists subsequent autopsy may reveal no valvular lesions In short a diagnosis of simple erosion can be made only at postmortem examination

Frequently, however during the course of a severe infection (acute gonorrheal sepsis pneumonia, or meningitis) when a murmur develops especially a basal diastolic one which is accompanied by embolic phenomena including petechiae in the skin or conjunctivae splenomegaly, and the isolation of a causative organism from the blood stream the diagnosis of acute *endocarditis* is justified In other words the diagnosis of acute endocarditis of whatever type can be made only if some signs of cardiac involvement are added to the preexistent murmur and fever

Acute Nonrheumatic Endocarditis—Of great interest is that type of endocarditis which apparently is not in any of the foregoing classes It is definitely nonrheumatic since microscopic examination of the heart muscle fails to reveal any evidence of rheumatic myocarditis Such cases are not uncommon Mitral lesions are the most frequent This is the type described by Libman and Sacks and later found to be a feature of disseminated lupus erythematosus The symptoms and signs of this disease are considered elsewhere

Acute rheumatic endocarditis is almost constantly associated with acute rheumatic fever and contributes special importance to

this disease Rheumatic endocarditis is discussed in detail in the section on Rheumatic Fever (p 435) See also section on Rheumatic Heart Disease (p 1003)

RALPH A KINSELLA

BACTERIAL ENDOCARDITIS

Acute Bacterial Endocarditis —*Etiology*—Acute bacterial endocarditis develops both as a complication of such infections as pneumonia in which immediate infection of valvular erosions is presumed to occur and as an infection of an old cardiac injury during the course of a bacteremia The source of the bacteremia is usually capable of recognition

Bacteriology—*Staphylococcus aureus Streptococcus haemolyticus* and *Pneumococcus* are the organisms especially prominent in the etiology of acute bacterial endocarditis The malignant character of the disease with its comparatively brief course is no doubt associated with the virulence of these bacteria Infection by the gonococcus and the meningococcus (in subacute cases) has also been described as well as by a number of other organisms

Morbid Anatomy—Besides the lesions typical of the endocarditis there are other changes characteristic of this acute bacterial form which are usually regarded as being embolic in origin They consist of hemorrhages about terminal vessels and subsequent infiltration with polymorphonuclear leukocytes These lesions occur in the skin as petechiae and on the surface of the kidney as rather coarse red spots (1–3 mm in diameter) usually with whitish centers Infarctions in organs such as the spleen lungs and brain are common Meningitis secondary to the brain lesions occurs frequently especially in the pneumococcal type

Symptoms—The type of onset is influenced by the character of the disease which caused the bacteremia Thus if endocarditis is a complication of lobar pneumonia it may be impossible to state exactly when the infection of the heart valve occurred A staphylococcus infection of the valve may have entered the body through a trivial cutaneous abrasion which may have healed before the patient was examined The signs of sepsis are more prominent than those of cardiac failure High fever of the remittent type a leukocyte count of 15 000 in streptococcal and staphylococcal infections or of 30 000 in pneumococcal infections frequent chills errant pains about the body, and violent cardiac action with a coarse murmur are the signs which indicate a bacteremia fed by an infected valve Occasionally besides petechiae hemorrhagic areas appear about the extremities Petechiae and emboli are much more rare in the acute than in the subacute variety of endocarditis Signs of meningitis are common and delirium is invariably established later in the disease Embolic pneumonia develops frequently The average length of the disease is four to eight weeks

The murmurs change gradually as the disease progresses become daily more coarse or new ones appear such as a diastolic murmur at the aortic area and are often accompanied by thrills in the later stages Purulent invasion of the tissues in the neighborhood of joints is a frequent occurrence in the pneumococcal and streptococcal types

Diagnosis—The symptoms of septicemia with special signs indicative of cardiac involvement are important in diagnosis The most conclusive evidence is contained in the blood culture this is invariably positive and may be the only means by which other sources of acute infection are excluded Similar cultures may also be obtained from the urine and spinal fluid

Treatment—The treatment for acute bacterial endocarditis is usually unavailing However recovery may be expected in some cases Reports of cure of gonococcal endocarditis with sulfanilamide have appeared and others such as the staphylococcal type may yield to treatment with sulfonamides Fever therapy either alone or combined with chemotherapy has given favorable results (cure) in several instances of gonococcal endocarditis

Subacute bacterial endocarditis, which was described by Schottmueller and also Libman in 1910 is more important than the acute type on account of its comparative frequency The average hospital of 200 beds usually admits several cases annually and in

localities where rheumatic heart disease is common, a larger number With increased facilities for clinical bacteriology it is being more frequently recognized

Etiology—Two factors are apparently essential in every case—a preexisting injury of the valve and a recent infection which may invade the blood stream In a typical case a patient with rheumatic valvular heart disease suffers from tonsillitis abscesses of the teeth or otitis media Under these conditions bacteria prevalent about the focal disease may enter the blood stream and invade the damaged valve Although both the aortic and mitral valves are commonly affected the former seems to be more often involved alone, particularly when aortic insufficiency is present A slightly damaged mitral valve as seen in the presence of mitral insufficiency, is more susceptible than the severely deformed lesion of mitral stenosis It is now recognized that subacute bacterial endocarditis may become grafted upon a fresh (active) rheumatic infection In older patients atheromatous changes in the aorta and aortic valve may constitute the preceding damage Congenital defects of the heart are also easily infected, notably defective interventricular septa, bicuspid aortic valve and patent ductus arteriosus (Botalli)

Morbid Anatomy—Minute perivascular hemorrhages occur throughout the body These are soon infiltrated by polymorphonuclear leukocytes then by lymphocytes and finally are resolved into minute scars They appear as crops of petechiae about the extremities and on the conjunctival and buccal mucous membranes On the surface of the kidney they produce what Libman has called a 'flea bitten appearance They are numerous in the brain and heart muscle and on endothelial surfaces It has been frequently assumed that these small lesions are bacterial infarctions No definite proof however has been furnished regarding their exact origin Other lesions appear which are larger and occur about the joints and produce redness and pain in circumscribed areas with occasionally an effusion into the joint cavity Of special interest are the partial thromboses of glomeruli which cause in this disease a peculiar form of glomerular nephritis Infarctions of the spleen are constant and cerebral embolism is common and usually terminal The vegetation consists of a mass of bacteria enmeshed in fibrinous material which is studded with neutrophils and lymphocytes It appears to develop as a result of implantation of bacteria on the previously damaged endocardium The idea has been advanced that fibrin protects the imbedded bacteria from the action of drugs This was the basis for using heparin in an effort to prevent the formation of the protective fibrin

Others believe that the vegetation develops as a result of bacterial plugging of fine capillaries in the previously damaged valve and then building up from the interior of the valve breaks through the necrotic material onto the free surface of the valve where fibrin is deposited on its surface Studies of vegetations both in human and in experimental cases seem to support the idea that the bacteria causing the infection of the blood stream are not those imbedded in the mass of pink staining material but rather the bacteria spreading upon the endocardial surface uncovered by fibrin This point of view would give fibrin a more beneficent role as far as the patient is concerned and would support the theory that the formation of fibrin should be encouraged rather than prevented

Bacteriology—The nonhemolytic streptococcus is responsible for 90 to 95 per cent of the cases of this type of endocarditis The gonococcus is an important causative organism among the remaining 5 to 10 per cent Unidentified gram negative bacilli and gram negative diplococci have been reported as the infecting organisms as well as *Staphylococcus albus* In unusual instances there are cultures usually obtained at autopsy of *Streptococcus viridans* in combination with *Streptococus haemolyticus* or with a fine gram negative bacillus but usually the field is occupied by a single strain Whatever the type of micro organism its virulence is always low A low grade serologic immunity is usually incited which may be demonstrated by the agglutination and complement fixation tests

Symptoms—The onset is usually indefinite The attention of the patient is not directed toward the heart as a rule but is diverted by the fever and lassitude to a consideration of other symptoms In some in

stances a severe infection of the throat or upper respiratory passages impresses itself and the patient feels that he has simply failed to recover from such an infection In some cases there is no history of recent infection and the mechanism of implantation cannot be visualized While there is a history of preceding heart disease in nearly all the cases this affection of the heart may not be known to the patient Thus the physician may be led to consider such diagnoses as tuberculosis pyelitis or anemia for several weeks before attention is finally focused upon the heart Very often a routine blood culture leads to a correct diagnosis early in the disease

The absence of a history of acute rheumatic fever is important because it serves to direct attention to the possibility of congenital defect. Syphilitic lesions in the aortic valve or aorta may become infected but much less frequently than rheumatic valvular deformities and congenital anomalies Most of the patients are between twenty and forty years of age with both sexes about equally represented

The fever is of the remittent type daily peaks of 103° F being common In the early days of the disease chills are not uncommon A feature of the fever is that there are phases during which the temperature is at a high level at some time during the twenty four hours and other phases of variable duration sometimes weeks when the temperature may be normal or nearly so This latter phase may arouse hopes that are soon to be frustrated The febrile phases often coincide with other evidences of activity such as splenic infarction or other embolic phenomena

The vegetations on the valves or on the walls constantly supply the passing blood with organisms which commonly induce emboli The murmurs resulting from these vegetations may be extremely faint in the beginning and the cardiac excitement is much more a sign of endocarditis As time goes on the murmurs become coarser or new ones develop and may be accompanied by thrills

The bacteremia is usually easy to detect However about 10 per cent of patients remain bacteria free especially those more than forty years of age as far as blood cultures are concerned It differs from the usual fatal bacteremia in being sustained at a certain quantitative level Some cases continue to yield a small number of colonies per cubic centimeter of blood others a great number but the amount in either case is nearly the same throughout the course of the disease.

The bacteremia itself is probably responsible for the peculiar ashen pallor (cafe au lait) for the gradual wasting for the intense exhaustion leading to a peculiar petulance on the part of the patient and for the anemia The white cell count is often between 12 000 and 18 000 although normal counts are not uncommon and the red cell count is frequently below 3 000 000 In some instances the leukocyte count is surprisingly low (4000–6000) The percentage of stab forms is high

The petechiae are often regarded as embolic in origin but there is no proof of this These little red areas measuring 1 to 2 mm. in diameter are found about the hands and feet and in the conjunctival and buccal mucous membranes They have a tendency to occur in crops as if representing immunologic or allergic phases Larger spots measuring 2 to 5 mm., slightly nodular and definitely tender are discovered by the patient about the small joints notably in the tips of the fingers and toes (Osler s nodes) These little episodes usually clear away in three or four days

Quite distinct from the petechiae in time are the infarctions A pain in the left upper quadrant with a suddenly palpable and tender spleen is evidence of an infarction in that organ Hematuria with bacteria in the urine may be regarded as evidence of such an event in the kidney Hemiplegia is not infrequent and is often of a terminal character Circulatory failure is uncommon during the course of the disease but is the terminal picture in about one third of the cases Focal embolic glomerular lesions are rarely of sufficient extent to disturb kidney function

Clubbed fingers are frequently seen in cases that have lasted several months. The spleen is usually enlarged palable often tender Other clinical features which are to be expected are nosebleed which in this disease is remarkably stubborn and which recurs often abdominal distention which resists the usual measures employed for this

condition and a mild, quiet delirium which often prevails for several days before death

Diagnosis —During any obscure fever with heart murmur the blood should be cultured repeatedly This is the most effective diagnostic procedure When signs of infarction or the familiar petechiae appear the diagnosis is easily made clinically Subacute bacterial endocarditis is to be distinguished chiefly from rheumatic endocarditis in which the blood occasionally contains the *Streptococcus viridans* Subsequent cultures are negative in rheumatic cases and the course of the disease with usual recovery confirms the distinction Furthermore the signs of myocardial affection are not as pronounced in subacute bacterial endocarditis as in acute rheumatic endocarditis However it is well to remember that both diseases may be present in active form

Prophylaxis —In order to avoid the disease anyone known to have valvular lesions should take precautions to prevent infections of the teeth tonsils and middle ear and should have existing foci of infection removed Before and after surgical removal of an infected focus sulfonamide therapy should be given Recognized coccal infections of the upper respiratory tract should be vigorously treated with sulfonamide Such patients should avoid exhausting work or exercise

Treatment —No form of treatment is successful It seems certain that no attempt should be made to *immunize* the patient by vaccines serums or nonspecific shock since such measures seem to shorten life Mercurochrome acriflavine and gentian violet have been used without avail An identical disease produced experimentally in dogs has been cured by intravenous injection of merthiolate and by oral administration of sulfanilamide but neither of these drugs has been successful in human cases There have been reports of favorable effects produced by various members of the sulfonamide group and by combination of one of these with heparin Favorable results have also been reported after the combined use of chemotherapy and artificially induced fever The use of one of the sulfonamides should be instituted and maintained in dosage sufficient to support a level of 5 to 10 mg per 100 cc blood The establishment of the diagnosis of patent ductus arteriosus is of high importance since infection of this congenital defect may be removed in a majority of cases by ligation of the duct Unfortunately other congenital defects may be present which are not as yet amenable to surgical treatment There are occasional reports in the literature of recovery from the disease following the use of sulfonamide with or without some form of fever therapy but the results are not constant nor in many cases are they permanent It is possible that infection of congenital defects can be more easily removed than infection of an old rheumatic injury It seems likely that the cure of the disease will eventually be found in the field of chemotherapy So far none of the evidence is conclusive

RALPH A KINSELLA

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CHRONIC VALVULAR CARDIAC DISEASE

Chronic valvular disease of the heart consists of chronic structural change in one or more heart valves Functional valvular defects should not be included under the term valvular disease' they must however be considered in discussing the differential diagnosis of organic defects Myocardial failure also should not be included although many textbooks in the past have included it particularly when the treatment of chronic valvular disease has been discussed Nor will acute and subacute inflammatory processes be considered since the term chronic

valvular disease refers to deformed valves and not to the disease causing the deformity These diseases which are acute and subacute endocarditis syphilis and arteriosclerosis are described elsewhere in this book

Incidence —Chronic valvular disease of the heart is common and is found universally It has been estimated that from 0.5 to 1 per cent of the community is affected This figure is too high for those parts of the world where the rheumatic infection is rare especially in the tropics but is not far from correct for regions where rheumatic fever and chorea are common such as the northeastern part of the United States of America and northern Europe especially Great Britain Accurate statistics are wanting

Lesions occur in both sexes and at any age from birth with its pulmonic stenosis to senility, with its sclerotic valves It is most common between the ages of fifteen and thirty years in those parts of the world where the rheumatic infection is rife and between forty and fifty five where syphilitic aortitis is common and the rheumatic infection rare At the earlier ages the female is more frequently attacked but as an accompaniment of syphilis and arteriosclerosis the disease appears more often in the male later in life

Chronic valvular disease is found in all races and countries but as has been already noted it is commonest in the colder temperate climates

Etiology —There are five types of chronic valvular disease congenital rheumatic syphilitic subacute and chronic infectious endocarditis and arteriosclerotic or calcareous The very rare involvement of the heart valves by neoplasms need not be included under the heading of chronic valvular disease Traumatic disease of the valves may occur and proved ruptures of aortic and mitral valves are on record but they are very rare and almost always superimposed on other diseases of the valves (rheumatism syphilis or arteriosclerosis) Tuberculous involvement is extremely rare

Congenital valvular disease consists almost solely of pulmonic stenosis which is a defect in fetal development the cause of which is not fully known Fetal endocarditis has been considered a reason for some cases of pulmonic stenosis but in other cases maldevelopment is doubtless the cause In a good many cases of so-called 'pulmonic stenosis the stenosis does not involve the valve itself but the upper (infundibular or outlet) portion of the right ventricle producing a subpulmonic or infundibular stenosis a centimeter or two proximal to the valve which in such cases is hypoplastic Congenital pulmonic regurgitation mitral stenosis aortic (or subaortic) stenosis and tricuspid stenosis have been reported but they are all much less common than pulmonic stenosis Lesser congenital abnormalities such as bicuspid and quadricuspid aortic and pulmonic valves need not be further discussed here except to say that bicuspid aortic valves are particularly liable to subacute bacterial endocarditis

Rheumatic valvular disease results from acute infection of the rheumatic type most commonly following rheumatic fever Vague pains in the joints or muscles tonsillitis and scarlet fever may also be followed by chronic disease of the heart valves of the rheumatic type In a certain percentage of cases probably about one quarter it is not possible to obtain a clear history of any of these infections Whether in these cases the infections themselves may be so slight that they are not noticed by the victims whether the infecting organism virus or toxin may gain entrance to the circulation without producing any noticeable local or general reaction or whether other disease may be responsible we do not know

The great majority of persons who have had rheumatic fever (about 85 per cent) develop chronic deforming valvular disease of the heart This generally begins in childhood is found most commonly in the decades from fifteen to thirty five years of age and is much less frequent after fifty years of age because many of its victims do not reach this age Uncomplicated chorea on the other hand is rarely followed by valvular disease

Syphilitic valvular disease results from a spirochetal invasion of the aorta which spreads down to the cusps of the aortic valve and even to the anterior cusp of the mitral valve It occurs much more frequently in males (nine out of ten cases) than in females and generally develops between

the ages of thirty five and fifty, some fifteen to twenty years after the primary syphilitic infection

Miscellaneous Infectious Chronic Valvular Diseases—Other varieties of infectious chronic valvular disease are less common Subacute bacterial endocarditis is not rare but since it is generally fatal ensuing chronic valvular defects are unusual Very rarely does a case of acute endocarditis due to pneumococcus gonococcus, meningococcus streptococcus staphylococcus influenza bacillus or other virulent organism survive so far as is known endocarditis constitutes a terminal infection during severe pneumonia meningitis influenza erysipelas or other septicemia Typhoid endocarditis is almost unknown Tuberculosis of the endocardium is also extremely rare once in a great while the presence of a tubercle on a heart valve is reported There is no evidence that such diseases as smallpox chickenpox measles whooping cough mumps diphtheria dy entery cholera plague typhus leprosy yellow fever or malaria are directly associated with endocarditis

Sclerotic or calcareous valvular lesions may occur in the old and middle aged They may be the result of atheromatous change or of deposition of calcium especially at the bases of the cusps (Monckeberg s sclerosis) like sclerotic or calcareous lesions in arteries or as not infrequently happens they may be superimposed on previous infectious injuries The aortic valve is affected in this way more often than any other valve

Morbid Anatomy—*The Valves*—CONGENITAL VALVULAR DISEASE consists generally in the narrowing of the pulmonic valve ring very rarely in stenosis of the tricuspid aortic or mitral valve Frequently the so called 'pulmonic stenosis' is located in the heart itself and involves the infundibulum of the right ventricle and not the valve This results in a two chambered right ventricle the terminal chamber being very small Pulmonic or infundibular stenosis is uncommonly an isolated lesion usually there are one or more other defects associated with it the most common of which is the combination of interventicular septal defect dextroposition of the aorta and marked enlargement of the right ventricle resulting in a clinical entity called the *tetralogy of Fallot*



Fig 119—Left ventricle opened revealing stenosed mitral valve Note the thickened short chordae tendineae and the coalescence of the valve cusps leaving the major portion of the valve like a circular shelf or diaphragm which can neither open nor shut

CHRONIC RHEUMATIC VALVULAR DISEASE consists of a scarring of the cusps and short

ening of the *chordae tendineae* There is a thickening of the lines of closure of the cusps later a stiffening and adhesion of the cusps to one another often with considerable deformity which may extend to the ring of insertion of the cusps and finally, a fusion of the whole valve into one fibrous mass which leaves but a narrow funnel shaped buttonhole or fish mouthed opening in the valve Hardening even to the point of calcification may occur especially in cases of long-standing aortic stenosis and mitral stenosis The most marked lesion is usually found in the mitral valve but extensive deformity is also common in the aortic valve while the tricuspid valve is not often much damaged and the pulmonic valve is very rarely deformed The relative frequency with which these various valves are attacked to any important degree is about as follows mitral 100 aortic 50 tricuspid 25 pulmonic less than 1

When the valve is so deformed that it can no longer close completely regurgitation or insufficiency is said to be present and when the deformity causes obstruction of the normal onward flow of blood, stenosis is the term used Any one of the four valves may show regurgitation or stenosis or both and not infrequently more than one valve is defective in a single individual The so-called functional regurgitation' or leaking and the relative valvular stenosis—due to dilatation of the ventricles the great vessels or the valve rings—are not included in this discussion since in themselves they are not evidences of chronic valvular disease although they often accompany it Anatomically speaking organic stenosis of a valve is almost impossible without some regurgitation and vice versa but preponderance of either stenosis or regurgitation often warrants the limitation of the clinical diagnosis to the single defect, for example mitral stenosis or aortic regurgitation Such a defect as organic mitral regurgitation can occur in rare cases without any mitral stenosis when shortened chordae tendineae prevent the valve leaflets from closing there also being a negligible degree of fusion of the cusps themselves

A normal heart weighing between 200 and 300 Gm should have valves with approximately the following circumferences

	Cm
Mitral	10
Aortic	7
Tricuspid	12
Pulmonic	8

If the mitral valve measures less than 7.5 cm in circumference the aortic valve less than 5 cm the tricuspid less than 8 cm and the pulmonic less than 6 cm., definite stenosis should probably be demonstrable clinically in a heart of average adult size

The fact that mitral stenosis of rheumatic origin is more common than organic mitral regurgitation has not been recognized until recently The occurrence of both stenosis and regurgitation of the deformed mitral valve is certainly more frequent than the appearance of either alone

Aortic regurgitation is about five times more common as a clinical finding in rheumatic heart disease than is aortic stenosis Often the two are combined and rather infrequently aortic stenosis occurs alone

Tricuspid regurgitation is not so common an organic defect as is mitral regurgitation while tricuspid stenosis of clinical importance is rare both as compared to mitral stenosis and absolutely Slight scarring of the tricuspid valve probably sufficient to produce slight regurgitation or stenosis not demonstrable clinically is fairly frequent but extensive alteration in the valve is decidedly rare

Pulmonic regurgitation is extremely unusual in rheumatic heart disease Stenosis of the valve of rheumatic origin is also very rare

Often the mitral valve is the only valve diseased after a rheumatic infection but in about two fifths of the cases with mitral involvement the aortic valve is also affected Very few of the cases showing aortic valve disease of rheumatic origin have no demonstrable mitral valve disease When the tricuspid valve which is rarely involved alone is affected it is almost always damaged at the same time as the mitral valve and the injury is sometimes accompanied by disease of the aortic valve in addition Pathologic examination shows that in 20 to 25 per cent of the cases of mitral disease there is tricuspid disease which is not demonstrable clinically The pulmonic valve in rheumatic infection is never the only valve affected

Recurrent attacks of rheumatic endocarditis are so common that the valves may bear the scars of several lesions Generally a progressive crippling develops to cause marked deformity of the valves in such cases At times postmortem examination reveals a row of fine nodules at the line of closure near the edge of the valve which is indicative of an *acute rheumatic endocarditis, it may show* a thickened fibrous cusp already contracted with shortened, stiffened chordae tendineae *or it may show the acute process* superimposed on the chronic In some cases, Aschoff bodies (the typical submiliary nodules of rheumatic infection) have been found in the valve substance before any deformity at all has occurred

Chronic syphilitic valvular disease presents the pathologic picture of a progressive infectious process showing not only the scarring but also the acute changes The luetic lesion begins in the aorta just above the valve and in time extends down to the mouths of the coronary arteries and to the valve cusps themselves by way of the commissures Degenerative changes retraction stiffening fusion of the sides of the cusps with aortic walls widening of the commissures and finally even superimposed calcification may occur Aortic regurgitation *is the result and may be still further in*creased by a weakening and dilatation of the aortic ring As a matter of fact quite often in cases of luetic aortic regurgitation the valve itself is little if at all damaged the leak being dynamic or functional in nature due to the stretching of the aorta at the attachment of the valve Stenosis does not occur in the uncomplicated luetic aortic valve lesion With progressive involvement of the aortic valve rupture may occur though this *is less common with lues* than with bacterial endocarditis The loud basal systolic murmur heard over the aortic area in many of the hearts with syphilitic aortic valve disease is not caused by aortic stenosis or by aortic roughening but by dilatation of the aorta Rarely the syphilitic process may by encroaching on the anterior cusp of the mitral valve produce slight deformity of that valve but there probably is no primary syphilis of the mitral valve Neither is there a *primary* luetic lesion of the tricuspid or pulmonary valves although unusual cases of syphilis of the pulmonary artery are on record

Other infectious valvular disturbances involve the valves in a variety of ways In the case of *acute bacterial endocarditis* there is generally extensive ulceration and formation of vegetations the edges of the valves are fringed at times with masses of bacteria and fibrin in various stages up to full organization Any one of the valves may be attacked but the mitral and aortic are the ones involved most frequently Embolism from the vegetations is common The valve cusps may be extensively ulcerated and perforated and even the chordae tendineae may be ruptured These extensive lesions are caused by staphylococcus streptococcus pneumococcus meningococcus and gonococcus Recovery from such disease is rare the lesions heal with great scarring and deformity *of the valves The right side of the heart is* involved in about 25 per cent of the cases of acute bacterial endocarditis and oftener when there is congenital heart disease

Subacute bacterial endocarditis due to the *Streptococcus viridans* and rarely to the *influenza bacillus* or *gonococcus* is of different nature the lesions being more discrete less extensive and fulminating and practically always involving the wall of the *auricle or ventricle in addition to the* valve cusps Subacute bacterial endocarditis is almost always superimposed on abnormalities already caused by rheumatic endocarditis or congenital defect it rarely attacks normal valves The typical lesion is a vegetation larger than in rheumatic but smaller than in acute bacterial endocarditis consisting of bacteria blood platelets and fibrin invaded by leukocytes The process extends apparently by contiguity *Here again embolism is common* and glomerular lesions in the kidneys with hematuria are frequent The scars formed in the uncommon recovered cases are quite similar to those of chronic rheumatic valvular disease but are more extensive they often involve the auricular and ventricular endocardium

Arteriosclerotic (calcareous) valvular disease appears in middle and old age often superimposed *on chronic* infectious or congenital valve lesions It may occur in otherwise undamaged valves the mitral and aortic being most commonly *involved* espe-

cally at their bases At times the resulting calcification may bind one or both of the mitral cusps by solid brittle chordae ten dineae to stony masses in the papillary mus cles and rocky projections may even pro trude from a stenosed aortic valve into the lumen of the aorta or downward into the muscle of the interventricular septum Frequently only the ring of valve attachment is the site of calcification What percentage of the patients with calcareous valve changes have previously had valvular disease we have no sure means of determining at the present time but it is probable that most of the extensively stenosed valves have been deformed before the calcification has oc curred

The Effect of the Valvular Disease—The effect of chronic valvular disease on the heart muscle and cardiac cavities is of course important Aortic stenosis and aortic regurgitation throw a great strain on the left ventricle and cause hypertrophy *Aortic re gurgitation* is somewhat more important in this respect than is aortic stenosis some of the largest hearts ever recorded (900–1000 Gm and more) have been the result of it The *cor bovinum* usually indicates aortic regurgitation Not only does the left ven tricle hypertrophy when there is aortic regurgitation but its cavity becomes enlarged (primary dilatation) to take care of the reflux of blood from the aorta during dias tole Apparently dilatation and hypertrophy in these cases go hand in hand *Aortic stenosis* may produce much or little hyper trophy of the left ventricle and if uncom plicated by aortic regurgitation no primary left ventricle dilatation secondary dilata tion occurs when heart failure sets in Aortic regurgitation complicated by moderate aortic stenosis is sometimes much less of a burden for the heart than aortic regurgitation alone A fact of much interest and importance is that when the left ventricle fails slowly or repeatedly in chronic aortic valve disease the increased pulmonary blood pressure causes the right ventricle to hypertrophy also and in rare cases of aortic valve disease with this evolution the right ventricle may be relatively more enlarged than the left ventricle itself

MITRAL STENOSIS throws a strain on the left auricle and right ventricle and therefore when this valve defect is well marked there is dilatation of the left auricle with thickening of its muscular wall, and hypertrophy of the right ventricle Eventually even the right auricle may feel the burden too and respond with dilatation and hypertrophy The left auricle, being affected first may as sume enormous proportions and cases are on record in which its bulk was larger than that of all the rest of the heart its capacity in creasing even to 1000 cc or more (normally about 125 cc) The right ventricle may grow to equal or to surpass the left ventricle in weight The left ventricle is little affected

MITRAL REGURGITATION throws a strain not only on the right ventricle and left auricle but also on the left ventricle which grows heavier and dilates in order to accom modate the extra blood which it takes in to compensate for the leak back into the auricle It is often true that the heart is more enlarged by combined mitral regurgita tion and stenosis than by preponderant mitral stenosis alone for this very reason With slight degrees of mitral regurgitation however there is little change in the weight of the ventricles or in the size of their cavities

PULMONIC STENOSIS is a great burden for the right ventricle and secondarily affects also the right auricle causing both to hyper trophy and dilate often to a marked degree before failure sets in there is uncomplicated right ventricular hypertrophy PULMONIC REGURGITATION is very rare the strain which is entirely on the right heart chambers pro duces dilatation and hypertrophy

TRICUSPID STENOSIS causes right auricular dilatation and hypertrophy and if marked engorgement of liver and great veins acting almost as does chronic constrictive pericar ditis TRICUSPID REGURGITATION affects the right ventricle and right auricle producing both hypertrophy and dilatation The effects of tricuspid stenosis *per se* are practically always accompanied by those of the accom panying tricuspid regurgitation and mitral stenosis so that both right ventricle and right auricle are considerably enlarged

Pathologic changes in other organs are not usually due primarily to chronic valvu lar diseases of the heart but rather to con gestive failure (acute or chronic passive congestion) or to infectious processes (em

bolism) Pulmonary vascular engorgement is however a common finding in mitral stenosis without demonstrable heart failure, and in such cases pulmonary 'apoplexy with a variable amount of hemoptysis is not rare Furthermore chronic stenosis of the mitral or tricuspid valve if marked and even without failure of the myocardium usually causes by obstruction alone chronic engorgement of the liver which sometimes leads to cirrhosis Pulmonary or cerebral or other peripheral infarction from embolism due to intracardiac thrombosis may be the first event to reveal the presence of chronic valvular disease (especially mitral stenosis)

Symptoms —There are no symptoms characteristic of chronic valvular disease Practically all the symptoms recorded in the old textbooks are those of heart failure or irritable heart the nervous heartache in mitral stenosis or aortic regurgitation anginal pain dyspnea palpitation (due to forceful heart action premature beats paroxysmal tachycardia or auricular fibrillation) cough weakness and fainting Even extensive damage of the valves for example, well marked aortic regurgitation occasionally produces no symptoms at all In such cases the myocardium is neither fatigued nor irritable Therefore the clinical diagnosis of chronic valvular disease must depend on physical signs and the results of instrumental tests

There are five symptoms however that may be traced more or less directly to valvular disease (1) heart consciousness is often caused by marked cardiac enlargement as in aortic valve disease (2) there may be a sensation of excessive arterial pulsation throughout the body with aortic regurgitation, (3) there may be dizziness faintness or even syncope due to cerebral anemia, in some cases of marked aortic stenosis (4) there is often dyspnea on effort and there may even be attacks of pulmonary edema and of cardiac asthma due to over distention of the pulmonary blood vessels in mitral stenosis the severity of such symptoms being dependent on the degree of the stenosis and on the grade of effort or excitement or other strain such as the onset of the tachycardia of auricular fibrillation, and (5) the liver and abdomen may become uncomfortably congested when there is marked tricuspid stenosis

Signs of Chronic Valvular Disease Discovered by Physical Examination and Laboratory Tests —In the discussion of the diagnosis of chronic valvular disease the valve lesions will be considered first individually and then collectively

Mitral Valve Lesions —Mitral valve damage (STENOSIS) is proved by an apical diastolic murmur with or without a thrill which begins a brief interval after the second heart sound in the absence of aortic regurgitation or other cause of marked left ventricular dilatation * There may or may not be a presystolic crescendo murmur at the end of it This is probably the only positive evidence of a mitral valve lesion that we possess There are many signs that indicate the probability of mitral lesions but do not prove them A very loud blowing or rough systolic murmur masking the first sound heard best at the apex and transmitted well to the axilla and to the back is fair evidence of mitral damage with REGURGITATION particularly if there is also a systolic thrill palpable at the apex provided there are not present causes of cardiac dilatation to produce functional regurgitation such as anemia infection or heart failure With a rheumatic history and some enlargement of the heart a loud apical systolic murmur is practically pathognomonic of mitral damage with regurgitation in the absence of pericarditis acute rheumatic cardiac infection ventricular failure with dilatation and aortic regurgitation If there is much cardiac enlargement as in hypertension with cardiac failure such a murmur often results from functional regurgitation, *though there is less likelihood of a thrill or of as much intensity of the murmur as in the case of a valve lesion*

Roentgenologic finding of a heart enlarged transversely with prominence of the left upper border is also good evidence of mitral valve disease the prominence of the shadow at the left upper heart border is due chiefly to enlargement of the infundibulum of the

* Rarely a very large left ventricular cavity without aortic regurgitation as in chronic adhesive pericarditis or acute rheumatic myocarditis may give rise to the typical mitral diastolic murmur with undeformed mitral valve This is probably to be accounted for as may also be the Austin Flint murmur by the abnormal change in the caliber of the blood stream as it enters the dilated ventricular cavity from the auricle

right ventricle and to dilatation of the pulmonic artery rarely to left auricular dilatation

The electrocardiographic finding of pronounced abnormal right axis deviation with prominent auricular complexes (P waves) in Lead I or II is excellent evidence of mitral damage in the absence of pulmonic stenosis Both of these changes come with advanced mitral stenosis as a rule and are corroborative evidence the apical diastolic murmur proving the condition

thrill may be found in nervous overactive hearts as well as *in mitral stenosis A reduplication* of the first sound at the apex and a prominence of the third heart sound should also cause suspicion of mitral stenosis These findings and the sharpness of the apical first sound indicate the need of exercise (or amyl nitrite inhalation) to increase the speed and force of the heart to bring out the mitral diastolic murmur with or without its presystolic accentuation in early or slight grades of mitral stenosis Recently a

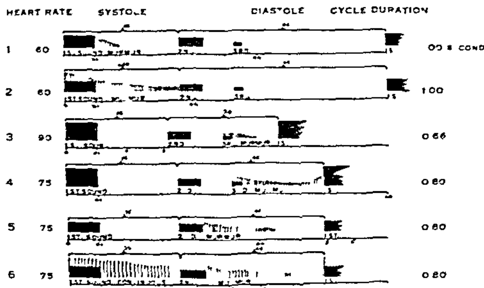


Fig 1?0—Heart sounds and murmurs graphically illustrated 1 A short systolic murmur heard at the apex indicative of mitral regurgitation When heard at the aortic area this murmur is usually indicative of slight dilatation of the aorta from hypertension or other cause When heard at the pulmonary area, it is entirely unimportant, a physiological functional murmur probably associated with some physiologic dilatation of the pulmonary artery 2 Long blowing systolic murmur masking the first sound and when heard at the apex indicative of a high degree of mitral valvular insufficiency In the aortic area, this murmur is usually harsh and may be found with aortic stenosis 3 Accentuation of the first heart sound and short mid-diastolic murmur at the apex indicative of slight mitral stenosis or dilatation of the left ventricle 4 The same as 3 except with a louder mid-diastolic murmur with presystolic accentuation indicative of a higher degree of mitral stenosis 5 A long blowing early diastolic murmur heard along the left border of the sternum, indicative of aortic regurgitation 6 Continuous murmur heard over the pulmonary valve area, indicative of patency of the ductus arteriosus

Marked accentuation of the second sound at the second left interspace near the sternum ($P_2 + +$) is usual in chronic mitral disease Auricular fibrillation constant in a young adult—under the age of forty years—generally means rheumatic heart disease with mitral involvement usually stenosis

Other signs that suggest the possibility of mitral disease include the sharp first sound at the apex with or without a very brief thrill in a heart not beating violently This short, so-called presystolic murmur and

very loud third heart sound close to the sternum in the fourth space has attracted attention the mitral diastolic murmur being found at the apex immediately following the third heart sound in many such cases this *loud third sound at the lower left sternal* border in mitral stenosis is probably due to dilatation of the right ventricle and gives rise when the heart rate is accelerated to a characteristic diastolic gallop rhythm presaging or accompanying right heart failure A pronounced presystolic murmur alone

without the mid diastolic murmur is rarely heard and unless the presystolic murmur is quite definite it should not be interpreted as *meaning mitral stenosis* Moreover, it should be remembered that when auricular fibrillation sets in, the auricles cease coordinate action so that *the presystolic* phase of the diastolic murmur of mitral stenosis disappears and leaves the telltale mid diastolic murmur behind Since auricular fibrillation is a very common condition especially in hearts with mitral stenosis this is a very important point to remember It shows the greater need of relying on the diastolic rather than on the presystolic murmur in the diagnosis of mitral stenosis Mackenzie *thought that the first murmur to appear in* mitral stenosis is presystolic in time and that an actual thrill also presystolic in time may precede the appearance of this murmur by some years it is the writer s opinion however that Mackenzie with his old fashioned monaural stethoscope failed to hear the mid diastolic murmur so characteristically found in most instances of early or slight *mitral stenosis and that he picked up only* the more advanced cases

The diastolic murmur already so frequently mentioned is of a characteristic type It begins an appreciable interval after the second sound and at once after the third sound when that is audible it is often *diminuendo* in character and is low pitched and rumbling It is best heard with the patient recumbent and by the use of the bell stethoscope The murmur is usually localized at or just inside the maximal apex impulse It is accentuated by exercise With *well marked aortic regurgitation the apical* diastolic murmur with or without presystolic accentuation may mean simply the so called "functional mitral stenosis described by Austin Flint Aortic regurgitation with a mitral diastolic murmur in a rheumatic heart should generally be considered as a combination of aortic regurgitation and organic mitral stenosis in a syphilitic heart as aortic regurgitation and 'functional mitral stenosis Thayer in 1901 reported a mitral diastolic murmur in forty five out of seventy four cases of aortic regurgitation which came to necropsy at the Johns Hopkins Hospital There was stenosis or other abnormality of the mitral valve in twenty eight of these seventy four cases so that by subtracting this number from the total figure we have a probable ratio of 17 46 or between one half and one third of the pure aortic regurgitation cases exhibiting the Austin Flint murmur

Other conditions suggesting the possibility of mitral valve damage are the history of rheumatic fever, especially if repeated attacks *have occurred cerebral or other* peripheral embolism (from left auricular thrombosis) in a young person, generally of the female sex hemoptysis in a young person without tuberculosis left recurrent laryngeal nerve paralysis and the mitral facies (cyanotic flushed face) with pulmonary congestion and in various stages of heart failure The pulse is often stated to be small and the systolic pressure low in mitral stenosis this is not infrequently so in cases of auricular fibrillation but it is certainly not always the case

Tricuspid Valve Lesions—Deformity of the tricuspid valve of any important degree is relatively rare and is usually difficult to diagnose The *frequency* of functional TRICUSPID REGURGITATION is great as compared with organic changes in the valve which produce regurgitation or stenosis Organic" regurgitation is rarely present without *stenosis its pathogenesis is the same* as that of organic mitral regurgitation Functional tricuspid regurgitation is a common *result* of right ventricular failure in very rare cases it may persist due to an irreversible dilatation of the tricuspid ring *Marked* TRICUSPID STENOSIS is manifested by a mid-diastolic murmur with or without a presystolic phase *which is localized* over the lower half of the sternum or just to the left of it Care must be taken to avoid confusion with a widely heard mitral diastolic murmur or with the early diastolic murmur of aortic regurgitation which is heard in the same place and also higher Mackenzie stated that he had heard the tricuspid presystolic *murmur* only three times Tricuspid stenosis is likely to be associated with auricular fibrillation and it *is rarely found in* advanced rheumatic heart disease without mitral stenosis Osler and Gibson stated that in a group of 173 cases of tricuspid stenosis this lesion occurred alone in only 12 it was associated with a mitral lesion in 97 with mitral and aortic

lesions in 58 with mitral and pulmonic in 3 and with pulmonic stenosis in 3

There are other signs suggestive of organic tricuspid valve disease A large liver may be present although Osler and Gibson say that it is not always enlarged with tricuspid stenosis Mackenzie looked upon pulsation of the liver with a marked wave due to the auricle as an evidence of possible tricuspid stenosis' but the auricles may fibrillate and the auricular wave will then disappear One of the features of these cases may be an enlarged nonpulsating liver without evidence either of cardiac failure or of alcoholic cirrhosis In such cases however one must consider chronic constrictive pericarditis Mitral stenosis alone may also produce chronic enlargement of the liver

Cyanosis marked in some cases and with a jaundiced tinge to the skin (the jaundice is due usually to a complicating pulmonary infarct) polycythemia dilated cervical veins increased dulness to percussion to the right of the sternum particularly in the third and fourth interspaces and a rather high abnormal prominence of the right auricular shadow with relatively clear lung fields by roentgen ray are all said to support the diagnosis of tricuspid valve disease but a fairly marked stenosis is necessary to bring out some of these findings The heart is enlarged transversely in tricuspid valve disease A superficial high pitched long rough systolic murmur maximal over the sternum at about the level of the fourth interspace and to the left rather than to the right suggests either organic tricuspid regurgitation or interventricular septal defect Electrocardiograms have shown abnormal right axis deviation partly at least because mitral stenosis is almost always associated Also when there is no auricular fibrillation the auricular complex (P wave) is increased in size The venous blood pressure is increased and there is usually a marked increase in the deep systolic jugular pulse (such pulsation is of course merely indicative of tricuspid regurgitation which may or may not be accompanied by any valvular deformity) Except for the frequency of auricular fibrillation the arterial pulse is not abnormal

Aortic Valve Lesions —A diastolic murmur beginning early and best heard down the left border of the sternum associated with the water hammer pulse is pathognomonic of AORTIC REGURGITATION This murmur may also be heard at the aortic valve area along the left border of the heart and at the apex but it should not be confused with the mitral diastolic murmur at the apex which is later in time and more rumbling in character Whether or not the cusp or cusps involved have anything to do with the variable transmission of the murmur is not known A musical diastolic murmur suddenly appearing after trauma or exertion or even spontaneously in rheumatic or syphilitic valvular disease usually means eversion of a cusp or very rarely in bacterial endocarditis a valve rupture

The marked water hammer quality of the pulse described by Corrigan is also pathognomonic of aortic regurgitation if there is an aortic diastolic murmur and if we can rule out marked peripheral vasodilatation Various suggestive phenomena such as the pistol shot heard over the great arteries for example in the groin the to and fro murmur on pressure over the great vessels (Duroziez s sign) and the visible pulsation or throbbing of the arteries of the head and extremities are dependent on the markedly increased pulse pressure due chiefly to the very low diastolic blood pressure This wide pulse pressure with very low diastolic reading is pathognomonic of aortic regurgitation except in cases of very marked peripheral vasodilatation The symptoms of ringing in the ears and vertigo sometimes complained of by patients with aortic regurgitation probably have their origin in the water hammer type of pulse An interesting phenomena observed by Hill and Rowlands in aortic regurgitation is the much higher systolic pressure in the femoral artery than in the brachial artery not dependent on hydrostatic pressure or the larger caliber of the femoral artery

Absence or weakness of the aortic second sound may be found in aortic regurgitation when it is accompanied by aortic stenosis The heart is always enlarged if there is much regurgitation and it is when regurgitation is marked that the greatest increase in heart size (*cor bovinum*) is commonly found The apex impulse is then often in the sixth or seventh space and out close to the anterior

axillary line Krehl, among others has however shown that very slight aortic regurgitation may occur without any obvious enlargement of the heart

The roentgen ray discloses a large heart increased in size downward and to the left with a rounded apex Increased excursion of the pulsation of the aortic arch is common in aortic regurgitation The aortic shadow is most increased in size if there is associated a syphilitic aortitis

In uncomplicated cases the electrocardiogram reveals markedly abnormal left axis deviation the most marked observed

Confusion of aortic with pulmonic regurgitation should be avoided by the rarity of the latter by failure to find signs of increased systemic arterial pulse pressure in pulmonic regurgitation and especially by roentgen ray and electrocardiographic study In cases previously diagnosed as having aortic regurgitation because of the finding of an early diastolic murmur along the left border of the sternum the roentgen ray may show marked prominence in the region of the pulmonary artery with marked pulsation of the hilus shadows of both lungs (the *hilus dance*) and the electrocardiogram may reveal marked preponderance of the right ventricle certainly not supporting the diagnosis of aortic regurgitation In such cases it is justifiable to make a diagnosis of pulmonic valve regurgitation but the opportunity to make such a diagnosis rarely arises except in occasional instances of marked mitral stenosis with heart failure where the pulmonic regurgitation is of functional nature I have encountered three cases in which I have felt justified in making the diagnosis of organic pulmonic regurgitation two of congenital origin and one acquired The diagnosis in the first two cases was confirmed by necropsy, the third case has not come to autopsy

A diastolic murmur heard over the sternum has been recorded as of venous origin transmitted down from a venous hum in the neck and has been encountered in exophthalmic goiter, such cases should present but little difficulty since in them the diastolic murmur is usually but part of a continuous murmur heard best in the neck

It must be added finally that a slight degree of aortic regurgitation is common and is not associated with any pulse or blood pressure changes If the diagnosis is not made until the late changes appear it is probable that at least 50 per cent of all cases of aortic regurgitation will be missed The diagnosis in many cases must be made from the murmur alone Functional regurgitation through the aortic valve was described by Corrigan and has been spoken of since by others but it is not common it may occur in cases with senile weakening of the aortic valve ring with or without hypertension

Aortic stenosis may be definitely diagnosed in the absence of any sign of an aneurysm on the discovery of a rough systolic murmur with a systolic thrill over the aortic area to the right of the sternum in the second interspace this murmur is widely transmitted especially to the vessels of the neck and to the cardiac apex Stokes noted that this murmur at times may be audible at some distance from the chest wall The pulse is generally small and anacrotic or plateau like or both a very important confirmatory finding The blood pressure is not remarkable except that there is often a low pulse pressure* if there is considerable regurgitation so that the stenotic effect is overbalanced there may be an increased pulse pressure and absence of the anacrotic and plateau characteristics The heart is usually enlarged downward and to the left as shown by palpation percussion and the roentgen ray but not to the extreme degree found in uncomplicated aortic regurgitation In aortic stenosis the aortic second sound is often absent or much diminished The electrocardiogram may show abnormal left axis deviation but mitral stenosis associated with aortic stenosis may neutralize the abnormal left axis deviation

Aneurysm and aortic dilatation may be confused with aortic stenosis of slight or moderate degree Pulmonic stenosis should not be confused with aortic stenosis because the systolic murmur of pulmonic stenosis though also loud and accompanied by a thrill is heard best to the left of the sternum and is not transmitted to the neck

Slight degrees of aortic stenosis may be

* It is however of considerable interest that an auscultatory gap is sometimes found in the process of blood pressure estimation in aortic stenosis

suspected when there is rheumatic heart disease with aortic regurgitation and a loud blowing systolic murmur at the aortic area transmitted to the neck even without a thrill Aortic stenosis overdiagnosed years ago is now quite often missed it is always to be considered as a possible and in colder climates common cause of a systolic murmur at the aortic area

Pulmonic Valve Lesions—Chronic valvular disease deforming the pulmonic valve is very rare Endocarditis of the pulmonic valve is almost invariably associated with mitral aortic or tricuspid lesions alone or combined PULMONIC REGURGITATION may be suspected by the finding of a murmur beginning early in diastole with or immediately following the accentuated second sound maximal in the second interspace just to the left of the sternum and extending down the left border of the sternum but the murmur of a slight degree of regurgitation through the pulmonic valve may be indistinguishable from that of slight aortic regurgitation since the position and character of the murmurs are almost identical and with a small amount of aortic regurgitation there may be no water hammer character to the pulse In such cases roentgenographic and electrocardiographic evidence should be helpful in indicating which ventricle shows the greater hypertrophy and which great artery—aorta or pulmonary artery—shows the greater pulsation With a moderate or marked degree of pulmonic regurgitation it is possible to observe fluoroscopically a definite water hammer pulsation in the pulmonary artery and the lung hilus shadows which at once differentiates pulmonic regurgitation from aortic regurgitation Organic pulmonic regurgitation may not be distinguishable from functional pulmonic regurgitation from the murmur alone The functional type occurs in cases of advanced mitral disease with much pulmonary engorgement The murmur of functional pulmonic regurgitation—due to the stretching of the pulmonic ring—is that described by Graham Steell Its frequency is a matter of some discussion It is said to appear and disappear with changes in the condition of the patient It may be difficult to distinguish from slight functional aortic regurgitation One should be hesitant about calling a slight early diastolic murmur heard along the left border of the sternum a Graham Steell murmur unless there is mitral stenosis of high degree and long standing Graham Steell himself found the pulmonic regurgitant murmur rarely Osler and Gibson say 'From the clinical standpoint so much that has been said about pulmonary regurgitation is either unproved or as yet incapable of proof that the subject should be approached with the greatest caution Pulmonary regurgitation is more often diagnosed than existent In several cases in which we thought it to be present in young persons the lesion proved to be aortic The rarity of organic pulmonic regurgitation should cause careful study before the diagnosis is made but functional pulmonic regurgitation (which is not diagnosable at autopsy) may as a matter of fact not be very rare I have encountered it in several cases every year its maximal audibility in the pulmonic valve area immediately following a markedly accentuated second heart sound is a most important clue

PULMONIC STENOSIS is a fairly common congenital heart abnormality but as the result of disease after birth it is exceedingly rare A loud systolic murmur in the second interspace to the left of the sternum with a systolic thrill not transmitted to the vessels of the neck is pathognomonic of pulmonic stenosis in the absence of signs of an aneurysm or of a plateau radial pulse Two types of congenital stenosis are described that occurring low and involving the infundibulum of the right ventricle and that involving the valve itself The former variety is likely to show the maximal murmur and thrill in the third left interspace and the latter in the second left space With any pronounced degree of stenosis there is considerable cyanosis chiefly as the result of the right to left shunt of venous blood through the defective ventricular septum An interventricular foramen is found in a large number of the cases of pulmonic stenosis (tetralogy of Fallot) Polycythemia and clubbing of the fingers occur with much cyanosis Enlargement of the heart to the left with the apex tilted up is shown by the roentgen ray Vaquez and Bordet call this the wooden shoe (*sabot*) shape The roentgen ray usually indicates hypoplasia of the pulmonic artery rarely a normal-sized

or dilated vessel The electrocardiogram indicates abnormal right axis deviation and it is in these cases of congenital pulmonic stenosis that the highest grades of right axis deviation are found Stenosis of the pulmonic valve acquired after birth should be distinguishable from the congenital type by the history of the case, by the evidence of other endocarditic lesions, and by the presence of pulmonic regurgitation also

COMBINED VALVE LESIONS —The combination of valve lesions causes a combination or a neutralization of the signs of the individual valve changes For example *stenosis* of the aortic valve cuts down and may completely neutralize the Corrigan pulse of aortic regurgitation Aortic regurgitation balances the right ventricular hypertrophy of *mitral stenosis so that the* whole heart may be symmetrically enlarged The characteristic murmurs of both lesions will be present in such a heart the early diastolic murmur of aortic regurgitation best heard along the left border of the sternum but often transmitted to the apex and the later rumbling diastolic murmur of mitral stenosis at the apex Sometimes an apparent difficulty may arise as to whether these murmurs represent the diastolic murmur of true mitral stenosis with the functional pulmonic regurgitant murmur of Graham Steell or the diastolic murmur of aortic regurgitation with the functional mitral diastolic murmur of Austin Flint Other data such as the type of ventricular enlargement (left or right sided) determined by electrocardiogram and roentgen ray, and the presence or absence of the Corrigan pulse or of pulmonary congestion should clear up such doubts quickly In rheumatic heart disease the two diastolic murmurs described above most often mean that there is both organic aortic regurgita*tion and organic* mitral stenosis More likelihood of error arises when one attempts to diagnose damage to three valves Osler and Gibson write As a rule the physician is in a safer position if he limits his diagnostic ambition *to two* valves Clinically when lesions of three or four valves are determined with accuracy mortifying *postmortem* disclosures are not unlikely to follow

Complications —The most common complications of *chronic* valvular disease are heart failure of the congestive type and irritability of the heart as shown by palpitation *and arrhythmia In the past* most accounts of the symptoms signs and treatment of chronic valvular disease have consisted largely of a recital of the evidence and treatment of heart failure In the case of aortic valve lesions the strain is chiefly on the left ventricle and it is that ventricle which tends first to produce such signs and symptoms of failure as edema of the lungs and Cheyne Stokes respiration Mitral stenosis exhausts the right ventricle first with the early appearance of hepatic and periph*eral stasis The pulmonary vascular conges*tion that commonly attends marked mitral stenosis either inconstant or in paroxysmal form is not to be ascribed to heart failure it is the result of the mechanical obstruction caused by the stenosed valve and so *is to be* strictly differentiated from the pulmonary vascular congestion of left ventricular failure Pulmonic stenosis is a rare cause for right ventricular failure The three valve lesions of aortic regurgitation mitral stenosis and pulmonic stenosis are the most serious of the burdens imposed on the myocardium by chronic valvular disease Even the strongest heart muscle may become exhausted eventually by such a strain Sometimes in these hearts the muscle is itself diseased and so unable to carry the burden long without trouble Neither the old view that the valve disease is the chief factor in the production of heart failure nor the modern view that weak muscle is the chief cause is sufficient Both factors play their parts inseparably though the strain due to the valve deformity is certainly the more important chronic factor and the acute or subacute rheumatic involvement of the myocardium is the more important *recurrent* acute factor

Irritability of the heart is common in chronic valvular disease Forceful uncomfortable heart beats (in aortic regurgitation particularly) paroxysmal tachycardia auricular flutter and auricular fibrillation (paroxysmal or permanent especially in mitral stenosis) and premature beats and *effort* syndrome with any of the valve lesions are frequently found but are not essential accompaniments of chronic valvular disease

Embolism into a peripheral artery is a complication which in a few cases accom

panies mitral stenosis Hemiplegia in young people may result from cerebral embolism from left auricular thrombosis in mitral stenosis Usually however embolism of cardiac origin results from infectious thrombi in subacute bacterial endocarditis or from mural thrombi over myocardial infarcts

Laryngeal paralysis with consequent hoarseness which is found rarely in marked mitral stenosis is probably the result of pressure on the left recurrent laryngeal nerve against the aorta by the pulmonary artery which is in its turn displaced by the much enlarged left auricle or right ventricle

One of the most serious complications of chronic valvular disease of congenital or rheumatic origin is the superimposed subacute bacterial endocarditis which is usually though not now invariably fatal

Differential Diagnosis —The commonest and most important conditions with which chronic valvular disease may be confused are those giving rise to the so called functional heart murmurs At this point I would like to recommend a revised nomenclature of murmurs in general Unless qualified the term functional does not distinguish between murmurs that are physiologic and murmurs that are pathologic and the term organic is customarily limited to the designation of murmurs that are the result of structural changes in the valves even though much more serious organic heart disease may be present in the myocardium with normal valves Hence the expressions physiologic and pathologic should I think be used primarily, the latter being subdivided into murmurs due to structural valvular and congenital defects and murmurs due to dilatation of heart chambers or great vessels which in turn may be the result of either cardiovascular disease or diseases of other nature such as anemia

A pathologic systolic murmur maximal at the apex without valvular disease may be heard when there is a dilatation of the mitral valve ring or dilatation of the left ventricular cavity with downward displacement of papillary muscles and chordae tendineae so that there is failure of the mitral cusps to close the left auriculoventricular ostium completely this may accompany cardiac dilatation as in primary heart failure or it may accompany adhesive pericarditis severe anemia or severe infectious diseases It is common in acute rheumatic infections which so often involve the myocardium and cause the left ventricle to dilate Sometimes a systolic murmur heard at the apex is due to the movement of air in or out of the lung tissue near the heart during systole such a murmur is intrapulmonary and should be distinguished from the other type of so called 'respiratory murmur which occurs in the heart itself only during certain phases of respiration The physiologic systolic murmur at the apex is generally less intense than the pathologic systolic murmur but not always so and slight murmurs do occur with organic mitral regurgitation of lesser degree A very loud blowing systolic murmur at the apex masking the first sound is much more likely to be evidence of organic than of functional mitral regurgitation unless the heart is large and dilated The smaller the heart the more likely it is that the *very loud* systolic mitral murmur is due to valve deformity Transmission of the apical systolic murmur to the axilla lung bases and elsewhere depends on the intensity of the murmur whether pathologic or physiologic well marked transmission of the murmur to the lung bases is evidence of its origin in mitral regurgitation in contrast to the systolic murmur of aortic stenosis Pathologic murmurs are more often transmitted because they tend to be louder However neither the time nor the intensity nor the quality of the apical systolic murmur due to mitral regurgitation determines with certainty whether or not the murmur is due to organic disease of the valve Other findings must decide that point if it can be decided at all in a given case An excellent discussion of systolic cardiac murmurs was published by Thayer in 1925

A physiologic systolic murmur maximal over the base of the heart just to the left of the sternum in the second intercostal space —the so called pulmonic area —is the commonest heart murmur of all It is heard in at least 50 per cent of all individuals in the recumbent position much less commonly in the erect position It seems to be a normal phenomenon but its cause is not known It is exaggerated in full expiration and the mechanism of its production may be related to that which normally causes reduplication

of the pulmonic second sound in full expiration—an increase in pressure in the pulmonary circulation which perhaps causes dilatation of the pulmonary artery or there may be compression or kinking of the pulmonary arteries with resultant murmur This kind of physiologic pulmonic systolic murmur is rarely if ever accompanied by a thrill probably on account of its low intensity Any circulatory weakness—particularly with severe anemia—tends to produce loud pulmonic systolic murmurs Congenital cardiac defects such as pulmonic stenosis patent ductus arteriosus and interventricular septal defect are to be differentiated from the physiologic pulmonic systolic murmur In the case of the congenital heart defects the murmur is usually intense and often accompanied by a systolic thrill while in addition with pulmonic stenosis there is generally cyanosis from birth with patent ductus arteriosus the murmur is continuous through both systole and diastole and with interventricular septal defect the maximal murmur is low in position generally at the fourth left costal cartilage close to the sternum

A pathologic systolic murmur maximal over the base of the heart just to the right of the sternum in the second intercostal space—the so-called aortic area —without valvular disease is quite common and is heard frequently when the aorta is dilated It does not come from roughening but from change in the caliber of the blood stream as it leaves the aortic valve and enters the dilated aorta Such dilatation of the aorta develops particularly in syphilitic aortitis in patients with hypertension and in cases with marked aortic regurgitation An aortic systolic murmur may not have obvious cause but it is rarely found in normal persons While aortic stenosis may occur without a systolic thrill or change in pulse pressure and shape it is something of a hazard to base this diagnosis on the murmur alone Physiologic aortic systolic murmurs do not produce thrills It should be noted that in some cases in which the aortic systolic murmur is thought to be functional there is doubtless present as its cause an actual slight aortic valve stenosis caused by calcification at the base of the valve cusps (the so called Monckeberg s aortic valve sclerosis)

A pathologic tricuspid systolic murmur which is not common should be found at the lower end of the sternum but may be masked by a mitral systolic murmur when there is dilatation of both mitral and tricuspid rings or of both ventricular cavities A tricuspid systolic murmur is not so frequent as a mitral systolic murmur although tricuspid regurgitation is common Probably the relatively low pressure in the right side of the heart accounts for the less frequent occurrence of a systolic murmur at the lower end of the sternum

A pathologic diastolic murmur maximal at the apex without valvular disease is occasionally found It resembles the mitral stenotic diastolic murmur exactly in time character and position but it is as a rule less intense and is not often accompanied by a thrill In well marked aortic regurgitation it is called the ' Austin Flint murmur and it has been thought to be due to a relative mitral stenosis resulting from the partial closing of the mitral value during diastole by the regurgitant stream of blood from the aortic valve impinging on the anterior cusp of the mitral valve But since exactly the same murmur is found now and then with left ventricular dilatation due to acute rheumatic myocarditis to severe anemia and even to heart failure in hypertension it is likely that the mechanism of its production is always the same Some patients with aortic regurgitation show the most marked dilatation of the left ventricular cavity known An unusual change in the calib the blood stream entering a dilated ventricle from a normal mitral valve account for this well known apical dias murmur *

A pathologic diastolic murmur whi heard best along the left border of sternum and at either the pulmonic aortic areas without valvular disease be due to either pulmonic regurgita (Graham Steell murmur) or aortic regu tation Both are very rare conditions an is almost always wiser to regard an e diastolic murmur which is maximal al the left border of the sternum as evidenc aortic regurgitation due to valve deform

* Heart murmurs are produced by marked cha in the caliber of the blood stream as it passes thr the heart, either forward or backward

The functional murmur is nearly always slight and is therefore not associated with much change of blood pressure but in character time and position it is indistinguishable from the organic murmur The pulmonic regurgitant murmur without pulmonic valve deformity occurs in marked mitral stenosis *with increased pressure in the* pulmonary circulation and consequently with abnormal pressure in diastole against the pulmonic valve the ring of which may itself be weak It is usually loudest in the second left interspace in contrast to the aortic regurgitant murmur which is loudest further down the left border of the sternum This type of aortic regurgitant murmur may be found in patients with systemic hyper tension and weakness of the aortic valve ring or in rare cases the latter cause alone may be responsible An important feature of the functional' diastolic murmurs at the base of the heart is that they tend to be transient appearing and disappearing with changes in the patient's condition Very rarely a Graham Steell murmur may be very loud and even accompanied by a slight thrill A pulmonic systolic murmur and accentuation of the pulmonic second sound precede the Graham Steell murmur

A pathologic tricuspid diastolic murmur without tricuspid valve deformity had not been recorded before the last edition of this work when I described such a murmur at the lower end of the sternum in a patient with a loud *Graham Steell murmur* who later showed at autopsy marked mitral stenosis pronounced dilatation of the right ventricle and a normal tricuspid valve

Other conditions to be differentiated from chronic valvular disease are *aortic aneurysm rare congenital defects such as coarctation of the aorta* and *pericardial friction rubs* An aortic aneurysm of the ascending or descending aorta may simulate to some extent aortic or pulmonic stenosis but the etiology and more marked thrills of valvular stenosis and the occasional finding of unequal pulses increased dulness at the base of the heart both by percussion and by roentgen ray occasional visible basal tumor or pulsation positive Wassermann reaction and vigorous arterial pulse sometimes seen in the neck with aneurysm help to differentiate the conditions The congenital cardiac defects mentioned above can usually be differentiated from chronic valvular disease by the history and by the unusual position and character of the murmurs Pericardial friction rubs are usually easily distinguished from the murmurs of chronic valvular disease by their scratchy near to *the ear character by their brief duration* (rarely more than a few days) and by the frequency of pericardial effusion coincident or following

Prognosis —Clinically pure *mitral regurgitation* due to valvular deformity of rheumatic origin if not of marked degree has a good prognosis Without further rheumatic infection or progressive deformity of the valve with ensuing stenosis and without the complication later in life of acute or subacute bacterial endocarditis the patient should live in full capacity for almost the normal span of life But it should be definitely stated that marked mitral regurgitation is a serious burden for the heart no less than is marked mitral stenosis and that mitral regurgitation of any degree with little or no mitral stenosis associated is not rarely complicated by fatal bacterial endocarditis

Mitral stenosis almost invariably rheumatic in origin is a very common condition in some parts of the world as in New England and it varies considerably in prognosis The lesser degrees may shorten life little if at all in fact proved cases have survived eighty years one such of my own recently died of pneumonia at eighty three Marked mitral stenosis is however serious it handicaps activity and is often fatal before or soon after the patient reaches adult life for the strain on the heart and lungs is great no matter what the condition of the muscle may be Auricular fibrillation and congestive failure with or without acute rheumatism eventually lead to death as a rule but now and then subacute (or acute) bacterial endocarditis or an intercurrent infection or pulmonary infarction is the cause of death Bacterial endocarditis rarely occurs on a markedly stenosed mitral valve it is much more common with lesser grades of deformity (regurgitation) which still permits some trauma to the valve tissue when the cusps close

Often the question comes up as to whether or not mitral stenosis or other chronic val

vular lesions should be a bar to *pregnancy* As there is no rule on which to base such a decision each case must be determined on its merits There is usually little difficulty during pregnancy and childbirth, unless the stenosis is marked or auricular fibrillation is present Both of these conditions—*i e* very marked mitral stenosis and auricular fibrillation—contraindicate pregnancy Auricular fibrillation especially is a serious complication Most serious of all is of course congestive heart failure, the pregnancy should not be terminated until after the congestive failure has been controlled, a well treated case may go on to term but should never be allowed to become pregnant again

Almost the same may be said of *rheumatic aortic regurgitation* of slight extent as of slight rheumatic mitral regurgitation, the prognosis is reasonably favorable The higher degrees of aortic regurgitation are however a great strain on the heart The victim usually does not attain middle age and he rarely survives it Death is caused by heart failure often induced by acute rheumatism or by acute or subacute bacterial endocarditis in youth

Syphilitic aortic regurgitation is always a serious sign—generally of advanced cardiovascular syphilis Patients with this lesion do not often survive more than a few years Death may ensue from rapidly progressive failure twelve to thirty six months after the discovery of the lesion but in occasional cases it is delayed much longer

Arteriosclerotic aortic regurgitation or aortic stenosis (Monckeberg s sclerosis) is usually but part of a general arteriosclerosis which may lead to death within a few years it can add a considerable burden to a heart often poorly supplied with blood

Rheumatic aortic stenosis has a better prognosis than a similar grade of aortic regurgitation and may allow survival to old age The presence of aortic stenosis if not marked may improve the prognosis of aortic regurgitation Once the heart begins to fail however the prognosis is poor

Tricuspid valvular disease is practically always complicated by disease of either the mitral or aortic valve or both and its prognosis depends mainly on that of the other valvular defects It is of interest that tricuspid stenosis when marked actually decreases the strain on the heart and reduces the gravity of the immediate prognosis

Pulmonic valvular disease is a serious condition whether congenital or acquired By far the most common lesion of this type is congenital pulmonic stenosis This condition even though compensated by some other defect like patency of the ductus arteriosus or interventricular septal defect is generally fatal early in life it may rarely allow survival to youth or even to middle age or beyond It handicaps activity very much and patients who do not succumb to acute infectious disease in childhood die as a rule of heart failure or subacute bacterial endocarditis in early adult life

Chronic valvular disease is thus a serious handicap and very often limits both the duration and activity of life Death comes generally because of heart failure often secondary to acute rheumatic myocarditis but may result from the complication of subacute bacterial endocarditis or other acute infectious disease against which the resistance is lowered

The most valuable prognostic sign in valvular disease is the size of the heart the larger the heart the worse the prognosis

Treatment—Very little need be said about the treatment of chronic valvular disease We are not concerned here with the treatment of its complications (such as heart failure either congestive or anginal) or of cardiac irritability represented by the arrhythmias

The treatment of chronic valvular disease itself to date has proved futile An attempt has been made to cut and thus to enlarge the stenosed mitral valve by *operation* but this method of treatment has been ineffective Only one or twice has such an operation been successful or even been followed by survival the mortality in a small group has been very high Actually there is little to be gained anyway in changing mitral stenosis into mitral regurgitation

No operative attempt has yet been made to correct the valve defects in the other more serious conditions—aortic regurgitation and pulmonic stenosis and it seems unlikely that such measures would be possible

There is no *drug therapy* yet devised to improve the condition of the scarred valves Only in the progressive changes in the aortic

valve which are due to syphilis is there hope from drugs at present and even in cardio vascular lues the antisyphilitic treatment may afford little benefit, sometimes in large dosage it may do harm and lead to early death Nevertheless careful therapy with potassium iodide and bismuth or arsenic should be attempted whenever possible that is in the absence of heart failure for life is sometimes prolonged thereby

Of course the prevention of further infections which are likely to damage the valves is of prime importance in individuals with chronic valvular disease Tonsillectomy avoidance of exposure to cold and wet and early use of salicylates in rheumatic fever and of the sulfonamides in bacterial endocarditis are worth while A change of residence from an unfavorable (cold and wet) to a favorable (warm and dry) climate is generally helpful in rheumatic heart disease and may be life saving Recently it has been demonstrated that the use of the sulfonamides during the winter and spring in children subject to recurrent rheumatic fever is protective by preventing infection with hemolytic streptococcus

Of the greatest importance of all is the campaign now under way to prevent the factors which produce chronic valvular disease The wiping out of rheumatic fever and chorea scarlet fever syphilis subacute bacterial endocarditis and presenile arteriosclerosis is more important than the discovery of surgical or any other methods of treatment

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DISEASES OF THE CORONARY ARTERIES

THE coronary arteries are subject to the same types of pathologic changes as are other arteries These comprise sclerosis due to atheroma and that associated with hypertension arteritis of various forms such as rheumatic and the common lesions of syphilis involving the coronary mouths (ostial narrowing) periarteritis nodosa thrombo angiitis obliterans rarely verrucous endarteritis aneurysms rupture and injury Sclerosis and syphilitic ostial narrowing are the only conditions which are at all common

C EGGLESTON

CORONARY SCLEROSIS

The great majority of lesions are due to (1) arteriosclerosis (atheroma) or (2) to the vascular thickening associated with chronic hypertension Often both types of vascular change are present to different degrees in the same heart This is almost always true following long standing hypertension Atheroma is common in the main coronary arteries the anterior descending branch of the left coronary (so called artery of occlusion) and only somewhat less frequently in the right coronary or its circum flex branch But narrowing or even obliteration of the lumen due to atheroma with

calcification may occur anywhere in the coronary bed Points of bifurcation are sites of predilection Several points of extensive narrowing or complete obliteration may be present simultaneously In such hearts the sclerotic process presumably has been of gradual development and as the local vascular narrowing progressed toward closure of the lumen at a given point anastomoses between neighboring coronary branches were *developing sufficiently to maintain a blood* supply adequate to preserve part or most of the myocardium Functionally the normal coronaries are end arteries as the intercoronary communicating arterioles of less than 40 microns in diameter are incapable *of carrying enough blood to maintain the* vitality of the myocardium when a larger branch is shut off acutely

Etiology—The cause of coronary atheroma *is* not yet known with certainty It appears often to be related to a disorder of cholesterol metabolism and is one of the natural concomitants of the aging process Although it may occur precociously it becomes increasingly prevalent in persons more than fifty years of age in whom it is the commonest of all causes of heart disease Whatever its ultimate cause it is generally regarded as a degenerative process associated *with physiologic aging It is irreversible and* gradually progressive

The etiology of hypertension as well as the pathologic vascular changes is discussed in a separate chapter As found in the coronaries these changes involve predominantly the smaller divisions and especially the arterioles Unless an associated atheroma is also present the intima is usually smooth and not likely to be the site *of thrombus formation*

Morbid Anatomy—The pathologic changes in the myocardium are much the same in both types and are the result of continued and usually progressive partial anoxemia and ischemia hence of impaired myocardial nutrition Whether because of atheromatous *narrowing or of the sclerosis* of hypertension the coronary circulation becomes less and less responsive to the demands of increased work The muscle fibers tend to lengthen and to hypertrophy as described in Diseases of the Myocardium (p 1048) These muscular changes are at first compensatory to increase the heart s contractile power The hypertrophy of the individual muscle fibers is not *accompanied* by an increase in their blood supply however and the larger fibers require both more oxygen and greater nutrition to perform their work The benign compensatory process soon becomes harmful and ultimately destructive through increase in the disproportion between blood supply available and the work performed so that either anginal or congestive heart failure begins to appear

Hypertrophy and dilatation of the heart may be absent or insignificant even when coronary atheroma is advanced in degree and present in multiple foci Commonly there is a moderate enlargement of the heart Occasionally this may be pronounced but in some cases there is usually some *additional* factor such as a valvular lesion or hypertension to explain the enlargement In the hypertensive form of coronary sclerosis on the other hand dilatation and hypertrophy are early and prominent pathologic features Such hearts may be truly enormous weighing 700 grams or more even without structural changes in a valve

The myocardium in either type of coro*nary sclerosis may appear normal upon* gross examination even where death was caused by myocardial failure This is commoner in the hypertensive form than in the atheromatous Frequently there is some visible scarring as shown by scattered areas of fibrosis Where atheroma has been the dominant cause with one or more *points of great* coronary narrowing or even complete obliteration of the lumen the areas of gross fibrosis are likely to be both large and widespread The fibrosis is seen microscopically to lie in and between the muscle fibers or to replace them not to be perivascular in distribution

Infarction of the myocardium is common in atheroma of the coronaries When fresh or *recent* the infarcted area is usually dark and hemorrhagic often with areas of yellow The tissue is soft and the area may be depressed below the surrounding muscle Later during healing the color changes to grayish or yellowish because of the invasion of

fibrous tissues or due to fatty changes Old or healed infarcts are seen as white usually depressed scars or when large they may be thin and extend through the entire thickness of the myocardium The latter may bulge and are then called cardiac or myocardial aneurysms An infarcted area occasionally ruptures Then a tear through the ventricular wall is usually readily visible The microscopic findings are those common to the several stages of necrosis and replacement fibrosis

The frequent sites of infarction lie in the areas supplied by the anterior descending branch of the left coronary, the right coronary or the circumflex branch of the left They are therefore to be seen in the anterior wall of the left ventricle the anterior portion of the interventricular septum or near the apex of the left ventricle in the posterior wall of the left ventricle and adjoining part of the septum or in the mesial portion of the same ventricle Infarctions may be single or multiple When multiple they may be of different ages from fresh to healed Infarction of the right ventricle alone is almost unknown but some extension of the infarct into the right ventricle is not infrequent specially where the apex or septum is involved

Incidence —Coronary sclerosis may occur even in advanced form without discoverable sclerosis in other arteries Some degree of sclerosis is usually to be found however in the retinae the peripheral arteries the aorta the kidneys or elsewhere if carefully sought Sclerosis of the coronary arteries has been found at all ages but it occurs mainly in the sixth decade of life and later It is more than three times as common in the male as in the female except in association with chronic hypertension when there is a relatively high incidence in women Both obesity and diabetes seem to predispose to coronary sclerosis possibly because of the disturbed lipoid metabolism in these conditions There appears to be a rather definite familial or hereditary tendency to coronary sclerosis so that several cases are often found in a single family One striking example from the author s practice showed three brothers to have died of acute myocardial infarction between the ages of forty and fifty years the only sister was hypertensive the father and one of his brothers were known to have died acutely of heart disease after having suffered from angina pectoris The mother succumbed acutely after a history suggestive of chronic hypertension, and two of the four grandparents also suffered acute death from heart disease while a third died of chronic Bright s disease and a terminal dropsy ' The average age at death decreased with each succeeding generation Chronic nephritis with hypertension appears to be an important predisposing factor in a smaller number of instances Few or no other factors are known materially to influence the occurrence of coronary sclerosis

Symptoms —Coronary sclerosis may be asymptomatic and is a fairly common necropsy finding in persons whose histories showed no symptoms pointing to disturbances related to the heart or circulation It is not rare to find one or more points of marked coronary narrowing or even complete atherosclerotic occlusion in the absence of a history of disability A few asymptomatic cases may be suspected on the discovery of changes in the electrocardiogram or upon x ray changes in heart or aorta Acute infarction may be painless and manifested only by an attack of acute edema of the lungs or of acute collapse apparently developing spontaneously Electrocardiograms may reveal the true cause and should be taken routinely

Gastro intestinal symptoms are often prominent and coronary disease may be overlooked when the major complaints are of indigestion or dyspepsia with eructations and flatulence or epigastric discomfort or pain *Hiatus hernia* must be kept in mind and excluded by appropriate roentgenologic examination because its symptoms may closely resemble those associated with coronary sclerosis including attacks of angina or even of myocardial infarction In some cases the symptoms suggest *disease of the gallbladder* Paroxysms of *spontaneous dyspnea* or nocturnal attacks resembling *asthma* sometimes of pulmonary edema may dominate the clinical picture and mislead the physician at least for a time The routine use of both x ray and the electrocardiogram will obviate many errors in diag

nosis Lastly among those without cardiovascular symptoms are persons past middle age who complain of progressive loss of energy, unexplained weakness and fatigability, and poor nutrition often combined with insomnia

The great majority of cases of coronary sclerosis are productive of symptoms of cardiac pain (angina pectoris or myocardial infarction) or of those due to congestive heart failure In the anginal group the pain is an expression of a transient local relative ischemia and, in accord with its cause is of short duration seldom lasting more than five to twenty minutes Where angina has been the dominant clinical syndrome extensive coronary sclerosis is usually found at autopsy There may be several healed scars of infarction and collateral coronary channels may be abundant But while these may be adequate to maintain enough circulation for moderate activity they may not be sufficient to meet extra demands The anginal syndrome as described occurs characteristically in response to conditions which increase the heart s work It may also be induced by tachycardia which is of rather frequent occurrence as a result of coronary sclerosis Anemia is often present in conjunction with arteriosclerosis and increases the susceptibility to angina Attacks of angina are frequently forerunners of acute infarction

C EGGLESTON

MYOCARDIAL INFARCTION

(*Coronary Thrombosis Coronary Occlusion*)

Advancing knowledge has made it desirable to revise our nomenclature by adopting the term myocardial infarction instead of the older and commoner ones of coronary thrombosis or occlusion Cardiac infarction is a satisfactory alternative term Myocardial infarction is most often the result of coronary thrombosis usually developing on the bed of an atheromatous abscess or on the surface of a calcified plaque but complete obstruction may occur without giving rise to any symptoms when collateral coronary circulation is adequate to prevent infarction Moreover infarction rarely may be caused by *coronary embolism* by the rupture of an atheromatous abscess in the wall of a coronary artery or by massive hemorrhage into such an abscess and from *too prolonged local ischemia due to the combination of focal coronary narrowing plus prolonged excessive work of the heart* as from tachycardia, and so on When the onset *of symptoms is sudden and apparently spontaneous* which is most common one may be correct in amplifying the diagnosis of acute myocardial infarction by the qualification *due to coronary thrombosis or acute coronary occlusion*

Symptoms—When acute cardiac infarction usually produces a group of symptoms *more or less typical* which permit its diagnosis The *sexes* are affected in the proportion of about seven males to three females The *onset* is spontaneous with *severe pain* in *the precordium* beneath the upper sternum or about the ensiform and upper epigastrium The pain is often described as constricting or in terms conveying the idea of weight pressure or compression The pain may remain rather localized or may radiate to the same regions as does the pain of angina namely to the sensory areas supplied by the first five thoracic segments of the spinal cord The pain is rarely relieved by rest or vasodilators and when severe morphine may not completely abolish it Accompanying the pain there are sweating pallor and often cyanosis causing an ashen appearance of the face The phenomena of shock or collapse are common appearing within a few minutes or hours Nausea and vomiting may ensue but it sometimes is hard to decide whether they are caused by the infarction or the opiate which usually is given promptly Untreated the pain persists for hours and even for a day or two

The *pulse rate* is usually increased well above 100 per minute and often the pulse is feeble and thready *Arrhythmias* may appear usually premature beats less often ventricular tachycardia auricular fibrillation or flutter Fibrillation and flutter are usually paroxysmal and vary in duration from a few heart beats to attacks lasting for several hours or days Rarely auriculoventricular heart block is an early event and

Adams Stokes attacks may result The blood pressure usually begins to fall within a few hours and may reach very low levels Both the systolic and diastolic pressure decline but the systolic falls proportionately more than the diastolic resulting in a lowered pulse pressure Occasionally the fall may be delayed for one or two days and very uncommonly there is a transient initial rise followed by a fall

Evidences of *destruction of tissue* appear on the first or second day They are fever of low grade only infrequently above 102° F by rectum which generally subsides within a week a moderate leukocytosis usually not over 15 000 a mild polynucleosis with a relative rise in the proportion of immature forms and an increase in the sedimentation rate of the red cells The elevated sedimentation rate usually persists much longer than the others of these phenomena and is considered to be one of the best guides to the progress of healing The other evidences of tissue destruction usually disappear within seven to ten days In 10 to 15 per cent of cases a transient pericardial friction rub may be heard

Examination of the heart reflects the pulse changes in rate and rhythm The apex impulse may be feeble or not felt at all The heart sounds are usually slapping and the first sound especially may lack its normal sustained tonal quality The sounds sometimes are loud and sharp More often they are faint and may even be scarcely audible The first sound may be split or reduplicated resulting in a gallop rhythm The second sound may also be split A systolic murmur is frequently heard at the apex but is not of special significance other than confirming myocardial weakness The lungs may remain clear throughout or they may show signs of any degree of congestion from a few basal rales on inspiration to a rapidly developing edema with profuse pink frothy sputum in which the patient may literally drown Secondary infection may take place in the lungs with a resultant pneumonia usually of the confluent lobular type or at times frankly lobar and due to one of the fixed strains of pneumococci When the infarcted area underlies the endocardium the resulting inflammation often leads to the formation of mural thrombi from which fragments may be broken off and cause embolization The brain the spleen the kidneys and upper or lower extremities are the usual sites

Diagnosis —Although diagnosis generally can be made on purely clinical evidence from the appearance of some combination of the symptoms given above electrocardiograms may be of the utmost assistance They may establish the diagnosis within less than twenty four hours in many cases They may provide decisive evidence when recorded serially in questionable cases They aid in localizing the site of infarction They establish the nature of the disturbances in the heart s rhythm or mechanism And often they are of much help in following the course of healing One or more of the precordial leads should be recorded routinely in addition to the conventional leads When a single precordial lead is used it is customary to take CFIV When taken very shortly after the onset the record may show no distinctive abnormalities

Localization of Infarct—When the infarcted area involves the anterior and apical portions of the heart including the left lateral wall it is likely to produce changes in the electrocardiogram of the Q_1T_1 pattern Lead I shows low potential of QRS and large Q wave There may be a Q in lead II and there are usually large S waves in leads II and III In recent infarction the R T junction and segment are displaced upward from the isoelectric level As healing begins the junction and segment return to normal and the T wave in lead I becomes a sharp V shaped inverted wave The precordial lead which corresponds to the Q_1T_1 pattern usually shows a large negative initial deflection or Q wave and the R T junction segment and the T waves are progressively altered exactly as described for lead I Such infarctions are commonly located in the course of the anterior descending branch of the left coronary artery *Infarction of the posterior and diaphragmatic walls* yields the Q_3T_3 pattern There is a large Q wave in lead III often also present in lead II QRS is of low amplitude in lead II In recent cases there is elevation of the R T junction and segment in lead II This is followed during healing by their return to the isoelectric level and by progressive change in T_3 which becomes V shaped and nega

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tive T_2 may follow T_3 The precordial lead is less consistently altered and may remain normal When altered there is likely to be a negative displacement of the R T junction and segments during the acute stages

Many changes in the electrocardiogram may result from coronary sclerosis with and without the occurrence of acute cardiac infarction These are seldom pathognomonic although they may be of great diagnostic value when related to the several clinical and other phenomena *A diagnosis should not be made on the basis of the electrocardiogram alone* Serial records are especially valuable when acute or recent infarction is suspected, both with relation to diagnosis and the progress of healing Many of the phenomena are transient some may remain more or less permanently Ectopic premature beats the tachycardias and auricular flutter or fibrillation of the auricles occur frequently Various grades of auriculoventricular block are to be found the lesser degrees being revealed only by graphic records Greater degrees often may be diagnosed from clinical changes in the heart rate and rhythm but even in these tracings are useful for confirmation or correction

The more significant features are to be found in the ventricular complexes These include waves of low potential involving either the first ventricular complexes the T waves or both Large Q waves may be found especially in lead III where they are suggestive when right axis deviation is absent Notching or splitting of the QRS group with its duration lengthened to $1/10$th of a second or over reveals some degree of defect in the spread of impulses through the Purkinje system There may be block of one branch of the bundle of His either left or right or a mixed type may be found Left bundle branch block is the type usually seen The R T junction may be displaced above or below the isoelectric line and so may be the R T segment The T wave may be inverted and of coveplane type or it may be of large amplitude and sharply peaked whether positive or negative It must be repeated that the value of such graphic records is greatest when they are considered in relation to the patient s history and other clinical findings and is least when they are considered alone an error too often made

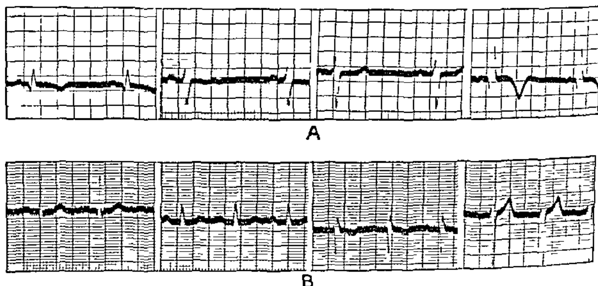


Fig 121 —Typical four lead electrocardiograms Leads read from left to right A is Q_1 T_1 type representing anterior or apical lesion B is Q_3T_3 type representing basal or posterior lesion

The development of roentgenkymography has provided a means by which it may be possible to demonstrate graphically *the location of an infarct* The destroyed area is revealed by a reversal of the direction of the movements of the margin of *the ventricular* shadow During ventricular *contraction* the infarcted region either moves outwardly or shows little or no motion Recently Master and others have stated that these same phe-

nomena can be seen by careful fluoroscopy This may prove of value but it is not yet well established

Attacks due to prolonged localized myocardial ischemia may appear in coronary sclerosis and present a clinical syndrome similar to that just described but different enough in fundamental features to be distinguished from infarction There is usually some closely related precipitating cause such as surgical or other type of shock acute severe hemorrhage operation, prolonged anesthesia or other condition which lowers blood pressure and lessens coronary blood flow Or they may be induced by increased work of the heart in excess of available increased blood supply for example by paroxysmal tachycardia intense emotion excessive physical effort and others Attacks of this type last longer than those of angina pectoris and unlike those due to myocardial infarction *they are not accompanied by evidences of destruction of tissue* The diagnosis of infarction should not be made in the absence of fever leukocytosis relative polynucleosis relative increase in immature polynuclear cells or elevated sedimentation rate in any combination This syndrome has been called coronary failure but a better term should be found since coronary failure has been applied to other syndromes with equal justification If an attack is believed to be of such nature treatment should be instituted at once to assure as efficient as possible a coronary flow relative to the patient s needs The suggested measures are given under treatment It is believed that effective treatment carried out promptly may at times prevent actual infarction During an attack of coronary failure the electrocardiogram may show transitory abnormalities similar to those seen in infarction but these are usually fleeting and often are missed entirely

The majority of patients with acute infarction survive the first two or three days to enter the second period which includes the remainder of the first two to three weeks The clinical features during this period are quite variable but it is nevertheless a period of real or potential danger The processes of liquefaction and absorption of the destroyed muscle are taking place and scar tissue is being laid down by invading fibroblasts Clinically the symptoms are usually subsiding Pain has usually stopped or lessened greatly and the evidences of tissue destruction ameliorate During this period the greatest hazards are embolism rupture of the ventricle or the development of serious disorder of the heart mechanism

Premature beats are common They may arise in the auricle the a v node or the ventricle They often are unimportant but if very frequent or if they appear consecutively and arise in the ventricle they may portend ventricular paroxysmal tachycardia or even ventricular fibrillation either of which may prove fatal Fibrillation of the ventricles is seldom survived and often kills so rapidly that there is no time for treatment Auricular flutter or fibrillation may develop but is much less dangerous and generally can be controlled or stopped Brief paroxysms of auricular fibrillation terminating spontaneously are particularly common and of relatively little moment Auriculo-ventricular heart block with or without the Adams Stokes syndrome is seen occasionally Varying degrees of intraventricular block are seen in electrocardiograms they are evidence of extensive myocardial damage and sometimes make prognosis unfavorable

Rupture of the left ventricle through a recent infarct is unusual It leads to very rapid death generally from cardiac tamponade If the tear be very small bleeding may be so gradual that death is delayed for hours The author recently saw an example of this in which hemorrhage had been so gradual that portions of the clot in the pericardium were undergoing fibrosis The rent in the heart muscle was very small and the channel through it very tortuous

Embolism is usually secondary to the formation of mural thrombi in the heart It may involve the lungs brain spleen kidney one or more extremities or some other part of the body Pulmonary embolism may be acutely fatal or it may constitute a serious complication from which recovery is slow In the earlier stages of pulmonary embolism there may be alterations in the electrocardiogram which are transient but aid in diagnosis The most important of these are the development of large S waves in leads one and two depression of the S T segments in the same leads and diphasic or

inverted T in lead I They should not be confused with the changes which may result from additional cardiac infarcts Embolism to the brain is likely to cause hemiplegia, and to other structures or organs the typical and easily recognizable manifestations described elsewhere

Congestive failure may begin at any time during this early period and produces the usual train of symptoms It may prove rapidly fatal, but generally tends to become chronic Its response to treatment appears to be determined by the extent of myocardial injury and the amount of coronary reserve remaining At times recovery is rapid and nearly complete so that the patient is left with but little handicap In such instances progressive failure usually develops as the terminal phase of the disease

The course in the majority of patients is one of more or less rapid recovery with subsidence of symptoms during the initial three weeks Thereafter the patient is well started upon convalescence and is not usually in much danger During the later weeks clinical recovery is accompanied by the return of the electrocardiogram toward normal but some patients do not manifest this change their records remaining abnormal for years By the end of about six weeks healing is complete enough in most cases to allow the patient to begin some mild activity However risky it may have been patients sometimes recover fairly well despite lack of proper early rest and treatment

Differential Diagnosis—Acute myocardial infarction may be confused with acute perforation of a peptic ulcer or rupture of the gallbladder acute pancreatitis and rarely with other surgical emergencies Prompt and correct diagnosis is most important since surgical intervention is a life saving measure in the foregoing condition while it is almost uniformly fatal in cardiac infarction The electrocardiogram is often of the greatest aid in differentiation Rarely the early stages of a dissecting aneurysm of the aorta may cause confusion in diagnosis but an error is not immediately dangerous as the early treatment of both conditions is the same The electrocardiogram may be the same in both conditions although the electrocardiographic changes are usually more transient in aneurysm The pain in dissecting aneurysm frequently is severe in the lower abdomen and lower extremities due to involvement of the abdominal aorta and its major branches Sensory changes, usually variable are prone to occur in the same areas and the pulsations may be reduced in the femoral arteries Further the dissection may extend along one or more of the branches of the aorta and be reflected in symptoms referable chiefly to the kidneys or to the gastrointestinal tract

Prognosis—This varies widely in myocardial infarction Death may be sudden or very rapid in the initial attack The great majority of patients however recover Statistics vary but about 80 per cent of all patients survive In some series the mortality has been as low as 8 per cent Efforts to establish criteria to improve prognosis have yielded some data of definite value Patients may recover after the severest symptoms while on the other hand death may occur with few or no preceding symptoms nevertheless among large groups of patients the mortality is definitely greater in those with severe initial symptoms This is especially true of early severe shock marked cyanosis pronounced dyspnea high fever greatly increased heart rate and high leukocytosis Other phenomena suggesting a prognosis less favorable than average include gallop rhythm and congestive heart failure When such complications as infarction of the lung pneumonia cerebral embolism or peripheral embolism appear the gravity of outlook is increased Any type of irregularity exercises some unfavorable influence but this is slight except for patients with ventricular tachycardia or ventricular fibrillation in whom the prognosis is much worse because of the abnormal rhythm Cardiac infarction is somewhat graver in women than in men The prognosis becomes less favorable with increasing age In general the younger subjects have a better outlook and longer life expectancy than older persons

Despite the help sometimes afforded by the preceding considerations prognosis in myocardial infarction is often difficult to determine particularly early in the course of the disease and should therefore be guarded as mistakes are common In the end death is almost always due to heart

disease The majority succumb within five years but a few may survive for ten to twenty years or longer Somewhat more than half of the survivors are able to return to their previous work at least to some extent if not fully

Men survive longer than women and more of them are able to resume full activity Women are more prone to subsequent congestive heart failure than men possibly because of the high incidence of underlying hypertension More than one third of the survivors die of a subsequent infarction and less than one third of congestive failure most of the remainder die suddenly from causes related to the heart

Treatment —Complete physical and mental rest should be required from the onset even if the diagnosis is merely suspected This should preclude the patient s feeding himself or turning without help and is intended to relieve the heart of all extra strain and if possible to bring its work down to a level which can be met by the curtailed coronary blood flow Marked apprehension and pain require the use of morphine 0 015 to 0 03 Gm (gr 1/4–1/2) by hypodermic The acute infarction may be productive of reflex spasm in other portions of the coronary tree Atropine sulfate 0.8 to 1.25 mg (gr 1/80–1/50) preferably by the intravenous route *may diminish or check* the spasm Somewhat smaller doses may then be given subcutaneously at intervals of about four hours Aminophylline (theophylline with ethylene diamine) is also effective when injected slowly into a vein in a dose up to about 0.5 Gm (gr 7½) repeated if required every four to six hours These agents may be continued for one to three or more days as indicated Papaverine has been used for the same purpose The usual dose is 0 065 Gm (gr 1) every four hours by vein

The prompt administration of oxygen either by nasal catheter suitable face mask or in a tent often lessens the load on the heart overcomes cyanosis and dyspnea and diminishes pain In those cases in which there is pulmonary congestion or shock immediate provision of an oxygen enriched atmosphere may maintain cardiac function until such a time as collateral circulation is established When 100 per cent oxygen is given the physically dissolved oxygen is increased as much as 2 5 cc per 100 cc of blood and it is this increase in physically dissolved oxygen in the capillaries which are adjacent to the occluded artery that is responsible for maintenance of cardiac function In these instances the continuous administration of oxygen in concentrations of 50 to 100 per cent may be the most effective method of treatment Shock or collapse requires prompt application of heat and the slow intravenous infusion of 5 per cent glucose in physiologic saline solution may be valuable particularly where there has been profuse sweating or repeated vomiting Occasionally it suffices to administer the glucose by hypodermoclysis or rectal drip When acute pulmonary edema is present the same measures should be instituted except that glucose should be given in 50 per cent solution From 50 to 100 cc are administered into a vein and injected slowly The same volumes of 50 per cent sucrose or sorbitol may be used but glucose seems preferable and is usually available promptly Epinephrine should not be used for there is danger of causing serious or fatal accident by throwing the heart into ventricular fibrillation Epinephrine is also contraindicated in collapse with hemoconcentration

A small porportion of cases show congestive heart failure almost *from the onset* these patients may be given digitalis as described (p 1151) Otherwise digitalis is not indicated and should not be given

During the first few days diet is not a matter of concern The patient should be given enough fluids by mouth to compensate for losses if he can retain them Such food as is permitted should be bland and not productive of gaseous distention Individual meals should be small and frequent Later the diet should be light digestible tasty and of low caloric value especially where the patient is overweight The bowels may be neglected entirely at the onset After two or three days mineral oil simple saline laxatives or cascara may be prescribed in doses just sufficient for a daily easy evacuation Suppositories or enemata may be required At times the strain of using a bedpan may be much greater than that involved in having the patient helped to a bedside commode

After the need for opiates has passed, usually by the second or third day, sedation should be provided by one of the barbiturates or by bromide with or without chloral These may also be used to promote sleep when necessary

Disturbances of heart rhythm may arise at any time and require treatment Premature systoles may be ignored unless very troublesome or very numerous They are often suppressed by phenobarbital but are more effectively controlled by quinidine in doses of 0 25 to 0 5 Gm (gr 4–8) given four or five times daily Paroxysmal auricular fibrillation usually does not require treatment because of its transient character If it persists the use of quinidine in the preceding doses may check it Occasionally doses up to a total of 3 to 4 Gm (gr 45 to 1 drachm) per twenty four hours may be required Paroxysmal ventricular tachycardia should be checked promptly by quinidine for it may lead to ventricular fibrillation and death or induce congestive heart failure The routine use of quinidine as a preventative of both ventricular tachycardia and ventricular fibrillation has been advocated The author prefers the plan of testing each patient s reaction to quinidine as early as possible after the attack of infarction and then reserving its further use until need for it arises

Heart block is rare and the lesser grades need no therapy Occasionally it produces seizures of Adams Stokes syndrome The oral use of ephedrine in doses of 0 045 to 0 1 Gm (gr ¾–1½) repeated as often as every two to three hours may prevent the attacks When this fails the intramuscular injection of 0.5 to 0 1 cc (minims 7½–15) of a 1 1000 solution of epinephrine may be required Rarely it may be necessary to try barium chloride by mouth This drug should be given cautiously The usual dose lies between 0 03 to 0 06 Gm (gr ½–1)

Aminophylline and theophylline because of their ability to dilate the coronaries are used by many in the hope of improving cardiac nutrition hastening recovery and preventing acute local ischemia The evidence as to their value remains somewhat conflicting They are commonly administered in doses of 0 1 to 0 2 Gm (gr 1½–3) of aminophylline or 0 2 to 0.3 Gm (gr 3–5) of theophylline three or four times daily They are given by mouth and enteric coated tablets may be ordered if nausea be produced

During convalescence after the third week has passed the patient may begin to feed himself may turn in bed without help may have occasional visitors and usually requires little more than symptomatic treatment It may of course be necessary to continue digitalis if it had been required because of congestive heart failure Many advocate the long continued use of aminophylline Convalescence may have to be prolonged where there has been extensive damage congestive failure or other complications The average favorable course usually permits the patient to resume nearly normal activity within three months from the onset Less favorable cases may require a year of carefully guided convalescence and some of these never regain more than a limited degree of physical capacity Some patients remain chronic invalids Throughout the entire course every effort should be made to maintain high morale and an optimistic attitude on the part of the patient

C EGGLESTON

SURGICAL TREATMENT OF CARDIAC PAIN

The development of our understanding that actual or relative localized myocardial ischemia is the mechanism by which heart pain is produced has led to many efforts to relieve the condition surgically Three general plans of approach have been suggested First to reduce permanently the amount of work required of the heart For this purpose total ablation of the thyroid gland was proposed It has been tried in a sufficiently large number of cases to justify its virtual abandonment in favor of other procedures The pain was more or less effectively controlled in a considerable number of patients but in many of these the symptoms of myxedema were about as incapacitating as had been the cardiac pain or the congestive failure Either or both of these would generally return if enough thyroid were given to control the myxedema

The second type of operation seeks to

increase the blood supply to the myocardium Various measures for increasing vascularization through the production of sterile adhesions between the two layers of the pericardium have been tried but proved inadequate They have been abandoned by most surgeons Omental or muscle grafts were proved in animal experiments to produce some revascularization of the heart but only when the need for it was caused by reduction in the normal coronary flow The operation has been performed in a relatively small number of patients by Feil and Beck using portions of the pectoral muscles and by O Shaughnessy who employed omental grafts The results are not yet convincing and the procedure is still in the experimental stage

The third surgical approach has been to cut or destroy the nerves carrying impulses from the heart to the spinal cord thus severing the reflex arc for the production of referred pain and that leading to reflex arrest of the heart or the production of ventricular fibrillation and death The afferent fibers of these arcs pass through the upper five thoracic sympathetic ganglia and the corresponding rami communicantes They may be broken by the paravertebral injection of alcohol or by surgical section of the dorsal nerve roots Both methods have their advocates and both require particular training skill and experience Alcohol block which does not necessitate a surgical operation consists in the injection through long needles of 5 cc of 85 per cent alcohol into the immediate region of each of the upper five thoracic sympathetic ganglia and their rami communicantes to destroy the nerves In the hands of an expert the injection usually succeeds and carries almost no mortality However a severe alcohol neuritis of the intercostal nerves occurs in a majority of patients It usually subsides entirely in one or two months but while present may cause intense discomfort Pleurisy is produced in a few patients and occasionally a temporary pneumothorax Coronary pain is relieved in nearly half of the cases and the relief is lasting The relief is temporary in about 30 per cent more who then may be re injected or subjected to dorsal root section In these either nerve regeneration has taken place or destruction was originally incomplete There is failure in 10 to 20 per cent of cases Horner s syndrome may occur

Dorsal root section is far more certain in its results but also requires high surgical skill and entails an extensive surgical operation involving laminectomy Despite its extent the operation carries a minimal degree of risk It is perhaps more likely to produce enophthalmus narrowing of the palpebral fissure and contracted pupil (Horner s syndrome) than is alcohol block but the results are permanent

Choice of procedure rests with the physician and the patient after the merits and complications of both procedures have been well understood White and Smithwick say

Among the 74 patients treated by surgical and chemical denervation we have now followed a large number in whom all sensation of pain has been removed Yet these patients always have the sensation of an attack either from a sense of thoracic oppression without pain or from palpitation flushing or shortness of breath Direct surgical denervation should therefore be the method of choice for the patient with severe cardiac pain who is a reasonably good surgical risk Unfortunately the number of patients with the severest forms of angina pectoris who fall into the operable group is limited The author has observed several dramatic recoveries by posterior root section

C Eggleston

CARDIAC ANEURYSM

This is a sequel to myocardial infarction in about 85 per cent of all instances in which it is found It may be produced by the degeneration and healing of other lesions which cause destruction of the muscular wall of the heart such as gummas focal mycotic abscesses localized rheumatic necrosis and trauma or it may arise congenitally in a membranous septum It has been noted in less than 10 per cent of necropsies in patients who have had myocardial infarction The aneurysm is most frequent in the left ventricle near the apex or on the lateral wall The posterior wall is seldom involved The great preponderance of cases occurs in males more than forty five years of age that

is in the same age groups in which myocardial fibrosis coronary sclerosis and myocardial infarction occur

Pathology —*Pathologically* the wall of the aneurysm is thin and composed of fibrous scar tissue but occasionally a few muscle fibers are found There is *usually* a lining blood clot which *may* be *laminated* and organized This may contain *calcium or the* fibrous scar itself may be the site of calcification *The aneurysm* may be only a shallow bulge of the ventricular wall a larger protruding cavity or a prominent sac connected with the ventricular cavity by a neck or narrow opening Rarely the aneurysm may rupture and cause sudden or very rapid death, but intraventricular and systemic blood pressures are usually too low for this to occur

Symptoms are infrequent and not diagnostic There may be an increased area of precordial pulsation increased area of precordial dulness, and occasionally a pericardial friction rub A gallop rhythm or systolic murmur sometimes both a systolic and a diastolic murmur may be heard at the apex Auricular fibrillation is fairly common and paroxysms of ventricular tachycardia may occur Both of these arrhythmias are however frequent in coronary sclerosis hence are not helpful in diagnosis The electrocardiogram generally reflects the previous apical or anterior infarction hence is of the Q_1T_1 pattern Often there is little or no disability Congestive failure or angina pectoris is occasionally present

Diagnosis rests chiefly on the history of a previous infarction combined with one or more of the following x ray findings (1) enlargement of the left ventricle with deformity of its silhouette (2) a localized shadow not separable from that of the heart by rotation of the patient (3) absent or abnormal pulsations of the margins of the shadow, (4) calcium in the margin of the shadow X ray study should include examination of the heart in oblique as well as in postero anterior positions A large gas bubble in the stomach may reveal an aneurysm on the diaphragmatic surface of the heart which would otherwise not be seen Fluoroscopy is often more helpful than films but both should be used Roentgen kymograms are at times of value

Cardiac aneurysm usually does not develop in less than one to two months after an infarction Death usually follows within two years after aneurysm has been discovered It may be sudden or due to congestive heart failure or may result from a complication such as cerebral embolism There is no treatment for cardiac aneurysm but proper care of the patient with acute infarction may possibly prevent its formation

C EGGLESTON

SYPHILIS OF CORONARY ARTERIES

Syphilis of the coronary arteries is due to extension of syphilitic aortitis of the proximal portion of the aorta into the sinuses of Valsalva The coronary lesion involves their mouths and the adjacent 0.5 to 1 5 cm of the vessel wall Usually the lesion is confined to the ostia themselves which are narrowed or even obliterated by extensive infiltration and fibrosis of the intima and to a lesser extent of the media The adventitia is less often involved The process is seldom seen in congenital syphilis Prior to the development of modern antisyphilitic treatment ostial syphilis of the coronaries was a common late manifestation of the disease The *frequency* of its occurrence has been materially reduced, but it is still far commoner than it should be Its incidence varies so widely among different groups of the population that figures are misleading It is much commoner in Negroes than whites in males than females and in the poor than the well to do Syphilitic ostial stenosis is unusual in the absence of aortitis but often accompanies aortic insufficiency Either of these conditions reduces coronary blood flow more or less significantly and together they may cause marked reduction This reduced coronary blood supply is responsible for such diffuse myocardial fibrosis as may be found postmortem Further the hypertrophy associated with aortic regurgitation increases the demand for greater blood supply to the myocardium There is some increase in coronary circulation however through the development of collateral coronary *anastomoses* during the gradual *narrowing* produced by the productive inflammation about

the coronary orifices Both ostia are usually involved but where only one is affected it is almost twice as likely to be the right as the left Similarly the right is usually the more severely stenosed

Incidence —The incidence of syphilitic coronary and aortic disease in the adult lies between less than 5 per cent and more than 15 per cent There is usually a latent period of nearly twenty years between the chancre and clinical signs of coronary syphilis making the decade between forty and fifty years that of highest incidence of the disease Rarely the period of latency is less than five to ten years and it may even be as short as three years Serologic tests are positive in 80 to 95 per cent depending upon the efficiency of the laboratory but a single negative test does not exclude the diagnosis

Symptoms —It should be the goal of the physician to recognize syphilitic aortitis with or without coronary involvement before the advent of symptoms This appears possible as yet in only a very few cases The use of a serologic test should be routine in the first examination of each new patient A positive test or history should be followed by special study of the circulatory system clinically and roentgenologically to detect or exclude such signs as accentuation of the aortic second sound or of a hollow or ringing quality of that sound The diastolic murmur of aortic insufficiency should be sought carefully along with the vascular signs of that lesion Minor degrees of widening of aortic dulness *are very hard to detect The x ray* should be employed regularly using both the fluoroscope and teleoroentgenograms with the patient in several positions Special attention *should be given to the supracar*diac portion of the aorta Unfortunately this cannot be visualized clearly because of its location so that when widening of the shadow can be made out the process is already rather advanced But such routine careful investigation may detect the damage early enough to permit effective antisyphilitic treatment

The *development* of *symptoms* is usually abrupt Spontaneous paroxysmal dyspnea frequently nocturnal is a common initial manifestation or the onset may be with pain of anginal type and location This may occur spontaneous*ly or follow* excitement or exertion The pain may remain localized over the upper precordium or it may radiate just as the common pain of angina Radiation through the chest to the back seems to be more likely than is the case in angina due to other causes Response to rest and the nitrites may be prompt The pain is probably due to myocardial ischemia and anoxemia Some patients complain of a more or less constant dull boring or gnawing substernal pain which has been attributed to active syphilitic inflammation of the root of the aorta rather than of the coronaries The paroxysmal type of pain is always associated with narrowing of the coronary mouths

The common signs of aortic insufficiency are often present and marked enlargement of the heart is usually evidence that the coronary ostia are not completely obstructed Attacks of so-called cardiac asthma and of more advanced degrees of pulmonary edema are seen frequently Sudden unexpected death often closes the chapter even before the development of any signs of congestive heart failure It is presumably caused by reflex arrest of the heart or by ventricular fibrillation There are no characteristic changes to be found in the electrocardiogram but left axis deviation is usually present with aortic insufficiency

Congestive failure is a late development in most cases and is evidence of marked exhaustion of the heart s reserve For this reason as well as because of the irreversible *nature of the coronary lesions the response* to treatment is likely to be of short duration or it may be very limited from its beginning

Course —*Untreated patients usually die* within less than five years of the earliest positive diagnosis and in less than two years after the onset of symptoms

Treatment —Theoretically it should be possible to prevent the development of syphilis of the coronary arteries and aorta by the prompt and adequate treatment of primary syphilis This is a goal which has not yet been reached but one toward which we should continually strive Some patients do not seek treatment in the stage of the chancre or even after secondary manifestations have developed Some who accept *treatment in these* most favorable stages

refuse to continue to the completion of a cure After the passage of the primary and secondary stages treatment of the syphilis can still do much to prevent irreparable damage to the heart, provided it can be started before cardiovascular symptoms have appeared If they have appeared the course of the disease is usually but little influenced by specific treatment In a few cases the syphilitic process may be arrested and several years added to the patient's life

Specific antisyphilitic therapy instituted after signs and symptoms of aortic and coronary lesions have appeared must be administered cautiously and in modified form The iodides may be used alone for a few weeks Then small and slowly ascending doses of mercury or bismuth are to be given for about two months If these have been tolerated well neoarsphenamine or bismarsen may be administered on a corresponding scale of slowly ascending dosage No attempt should be made to use full doses at any time and arsphenamine is better not used at all Attempts at either rapid treatment or maximal therapy may be disastrous from the production of a Jarisch Herxheimer reaction in the root of the aorta or the coronary ostia with resulting acute closure and death Or too radical therapy may eradicate the syphilis but cause fatal scarring in the aortic root This has been called the Therapeutic Paradox by Wile

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CORONARY ARTERITIS AND EMBOLISM

Rheumatic coronary arteritis cannot be recognized unless it is accompanied by rheumatic lesions elsewhere The active form most often shows Aschoff bodies in the adventitia with the localized collection of polynuclear leukocytes and lymphocytes in and about the fragmented collagen Typical giant cells may be found in the older lesions Healing takes place with the formation of a dense scar Thrombosis is rare Healed lesions leave thickening of the vessel wall involving all three coats but the intima and adventitia are usually the most severely scarred The lumen is often much narrowed Where Aschoff bodies are present on opposite walls of a coronary they may narrow the lumen greatly but this is of rare occurrence

Sometimes rheumatic coronary arteritis and aortitis are responsible for clinical manifestations identical with those produced in syphilis The anginal syndrome may occur particularly in the more acute stages of rheumatic arteritis

Arteritis of the coronaries also is found in other diseases than rheumatic fever Among the commoner of these are diphtheria and scarlet fever the septicemias pneumonia and so on Its occurrence is of little clinical importance as it is seldom sufficient to produce symptoms and those which may be present are not distinctive Occasionally in pneumonia and somewhat more often in septicemia mycotic aneurysms may arise in the coronaries Any type of arteritis when affecting the coronaries may lead to the symptoms of angina pectoris or cause thrombosis and cardiac infarction but such accidents are rare

Periarteritis Nodosa —This is an acute or subacute inflammatory disease the etiology of which is unknown It affects chiefly arteries of medium size anywhere in the body including the coronaries which are estimated to be involved in as high as 70 per cent of cases The lesions in the coronaries are the same as have been described in other arteries When the coronary lesions produce symptoms they are the same as those already described for other forms of coronary arteritis They may be more or less masked by the other symptoms of this bizarre disease

Embolism of the coronaries may occur but it is quite rare The emboli are derived from endocardial lesions on the mitral or aortic valves in most instances but may arise almost anywhere in the body If the emboli are infected they may cause local abscesses or produce mycotic coronary aneurysms Occasionally such aneurysms rupture into the pericardial sac More frequently embolism into a coronary produces the characteristic picture of an acute myocardial infarction The clinical diagnosis of embolism demands the recognition of some source of emboli It is usually little more than inferential until and unless established at the necropsy table

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MISCELLANEOUS PATHOLOGIC CONDITIONS

SYPHILIS OF THE HEART

In this presentation only tertiary syphilis of the myocardium will be considered as syphilitic aortitis with its complications aortic regurgitation involvement of the orifice of the coronary arteries and aortic aneurysm are discussed in another section (p 1166)

History.—The first gumma of the heart was reported in 1845 by Philippe Ricord an American born French syphilodermatologist Subsequently Virchow described tertiary syphilis of the heart as either fibrous or gummatous in type however the former is probably indistinguishable from fibrosis due to coronary artery disease Warthin found myocardial lesions in 40 to 60 per cent of the hearts of syphilitic patients and spirochetes in the heart muscle of the majority of these cases but these findings in acute syphilitic myocarditis have not been confirmed by other investigators

Morbid Anatomy.—Gummatous myocarditis occurs in two forms (1) diffuse miliary or submiliary gummatous myocarditis and (2) localized gummatous myocarditis the so-called cardiac gumma Both occur in congenital as well as in acquired lues Sohval has collected all the authentic cases and found that there were only seven reported instances of the diffuse form, and ninety seven of the localized gummatous type The *pathology* of the gummatous lesion in the heart does not differ from that of gummas in general The gumma may be solitary or multiple Remnants of degenerated muscle fibers in the central necrotic area may help to differentiate the gumma from a tuberculous lesion of the heart The gumma may involve the bundle of His or its branches causing various grades of heart block it may interfere with valvular function by direct invasion or may cause a pseudo stenosis of the valvular orifices by pressure upon them The gummas may caseate excavate and thus form cavities in direct communication with the chambers of the heart They may cause epicarditis rupture of the papillary muscles perforation of the interventricular septum or rupture of the heart through aneurysm of the heart wall In that way they may be a cause of sudden death

DIAGNOSIS.—Clinically syphilis of the heart is rarely diagnosed with certainty but under favorable conditions its presence may be suspected and the patient be given the benefit of treatment As the most frequent site of the gumma is in the left ventricular myocardium (Stockman) and usually at the base of the interventricular septum it may cause heart block of any grade by involvement of the A V bundle or its branches and thus the diagnosis may be suspected in a syphilitic patient Again the gummatous process may compromise or by extension invade a valvular or subvalvular region thus causing valvular pseudostenosis or insufficiency this has occurred in the region of the pulmonic aortic tricuspid and mitral valves—in order of frequency If a bizarre stenotic murmur is heard in a syphilitic patient and especially if this is associated with unexplained roentgenographic shadows along the cardiac margins a gumma may be suspected A positive Wassermann reaction

is not necessarily present in this condition Sohval states that when atypical cardiac findings are discovered in a condition known or suspected to be syphilitic, tertiary cardiac syphilis should be considered and one may add, appropriate antiluetic treatment should be instituted

Treatment —In treatment one should remember that the patient is a heart patient and that rest is important to avoid heart failure As in any case of cardiovascular syphilis it is wisest to begin specific antisyphilitic treatment with bismuth or mercury injections combined with sodium or potassium iodide in order to avert therapeutic shock later to select the arsenical least likely to give any untoward reaction and to postpone the use of the arsenical preparation until there has been time for heart muscle and elastic tissue to regenerate

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TUBERCULOSIS OF THE HEART

Tuberculosis may affect any part of the heart The most common type of involvement tuberculous pericarditis is generally secondary to tuberculosis of the lungs bronchi mediastinum or to general miliary tuberculosis The pericarditis may be fibrinous or fibrinocaseous in which case a pericardial friction rub will be a prominent sign or there may be an effusion either serofibrinous hemorrhagic or purulent The disease frequently runs a slow chronic course with formation of pericardial adhesions and partial or even total obliteration of the pericardial sac More detailed discussion will be found in the section on Pericarditis (p 1039)

Tuberculosis of the myocardium is relatively rare The heart muscle like other muscle seems to have a high degree of immunity to tuberculosis In overwhelming severe miliary tuberculosis especially in young people and children the myocardium may occasionally be involved and on post mortem examination may reveal miliary tubercles large tubercles or even diffuse tuberculous infiltration Infection of the bronchial and mediastinal lymph nodes or of the pericardium may progress by direct extension to the myocardium and involve any part of the auricles or ventricles Myocardial tuberculosis is not known to produce ulcerative lesions The *signs* and *symptoms* depend on the structures affected and the extent of involvement Generally the cardiac involvement is of a minor nature and is so overshadowed by the active tuberculous process elsewhere that diagnosis is made only at necropsy

Tuberculosis of the endocardium is very rare Occasionally in acute miliary tuberculosis autopsy discloses miliary tubercles in the endocardium or more rarely in the valves Very rarely a nonulcerating vegetative or fibrocalcareous lesion may be found There are no characteristic signs or symptoms *Treatment* consists of care of the tuberculous infection

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WOUNDS OF THE HEART

Wounds of the heart belong more to the domain of surgery They may be caused by *cutting instruments* as in stab wounds of the thorax by sharp objects such as paracentesis needles by bullets fractured bones etc Exploratory needles penetrating the wall of the heart do not usually cause fatal hemorrhage but may do so especially if the wall of the auricle is torn The whole cardiac wall need not necessarily be penetrated to produce severe symptoms The *chief danger is hemorrhage* not merely because of the large loss of blood but because overdistention of the pericardial sac may compress the auricles and prevent filling of

the heart during diastole resulting in tamponade of the heart Other serious complications are hemopneumopericardium purulent pericarditis empyema pyopneumothorax adhesive pericarditis and mediastinitis heart failure and possibly ventricular fibrillation The *symptoms* which lead one to suspect a wound of the heart complicating a wound of the thorax are those of precordial pain at times also abdominal pain and spasm of the abdominal muscles a pulsating stream of blood from the wound which may be foamy from admixture of air from the lung or the evidence of severe hemorrhage

The *physical examination* may reveal a pericardial friction rub a rapidly enlarging area of cardiac dulness due to hemopericardium or the presence of the characteristic water wheel murmurs of pneumohemopericardium With these there is usually all the evidence of severe internal hemorrhage With the development of cardiac tamponade the heart rate increases while the blood pressure and pulse pressure fall and the venous pressure rises The heart sounds become fainter and the area of cardiac dulness increases Stereoscopic x ray examination or fluoroscopy may locate a foreign body or missile in the heart

The *treatment* is largely surgical consisting of suture of the heart wound Recovery results in about 35 per cent of the operated cases Small transfusions of blood are also indicated Large branches of the coronary artery have been ligated with recovery as in a case recently reported by Davenport and Smith

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CONTUSIONS OF THE HEART

Contusions of the heart may be the result of direct trauma to the heart itself but are generally the result of trauma to the chest wall without any necessary penetration of the skin or any obvious superficial injury External violence such as a sharp or heavy blow on the precordium is capable both in experimental animals and in human beings of producing definite areas of contusion in the heart muscle by a process analogous to the mechanism which causes cerebral concussion The heart muscle is bruised with resulting hemorrhage and myomalacia and the pathologic characteristics of the scars of myocardial changes produced by coronary artery occlusion In recent years the so called steering wheel injury has become fairly common Here as the result of an automobile accident the driver is thrown forcibly forward so that his chest strikes against the steering wheel and his heart is bruised without any permanent injury to the bony thorax The *clinical signs* of such myocardial damage are very similar to those following coronary artery closure and may include the electrocardiographic changes characteristic of damaged heart muscle as well as the changes in heart rate heart sounds blood pressure temperature and leukocyte count which are associated with classic coronary occlusion Extrasystoles auricular fibrillation or other types of arrhythmia may result Within a period of a few hours to a few days following the trauma the patient generally experiences symptoms of cardiac pain and circulatory weakness which may gradually improve or may go on to eventual cardiac failure

The *diagnosis* rests on the combination of a history of trauma to the thorax with the development within a few days of symptoms and signs of myocardial injury

The *treatment* consists of rest sedation and the same general measures that apply in acute coronary artery closure Surgical interference is indicated only if hemorrhage or rupture occurs

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TUMORS OF THE HEART

Tumors of the heart are rare They may be divided into primary and secondary new growths *Malignant cardiac tumors* are rarely primary but usually attack the heart by extension from neighboring structures or by metastatic involvement The *primary neoplasms* reported have been sarcoma fibroma myxoma myxofibroblastoma, lipoma lymphangioma cavernous myoma melanoblastoma and rhabdomyoma The last mentioned is multiple and has been found associated with sclerosis of the brain and malformation of the kidneys The other tumors are more commonly found in the auricles (Link) The secondary metastatic growths found have been those originating from renal tumors melanosarcoma xanthosarcoma osteosarcoma chondroma thyroid tumors, and carcinoma New growths may invade the heart by direct extension along the pericardial sac *e g* sarcoma of the thymus carcinoma of the lung pleura or esophagus

Clinically tumors of the heart give no characteristic symptoms Occasionally a neoplastic growth in the left auricle may cause a narrowing of the mitral orifice and thereby simulate a mitral stenosis Evidence of pericarditis dry hemorrhagic or purulent may be found In a few cases the tumors have compromised the bundle of His and given rise to bradycardia and heart block A case reported by Krause and another by Ehrenberg gave evidence of their presence by x ray examination The diagnosis may be suspected if cardiac signs or symptoms such as auricular fibrillation develop in the course of malignant disease elsewhere in the body with signs of pericardial effusion especially hemopericardium obstruction of a large vessel and x ray evidence The prognosis of malignant cardiac tumors is hopeless

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PARASITES

The parasites which may occur in the heart are the echinococcus the *Cysticercus cellulosae* of *Taenia solium* and perhaps the *Trichina spiralis* They are all rare and their diagnosis almost impossible The echinococcus (hydatid cyst) occurs most commonly in the right ventricle and produces no symptoms unless the cyst bursts and thus gives rise to embolic infarcts in the lungs pneumonia or pleurisy or to a blocking of the pulmonary artery Sudden death has resulted from such rupture The cysticercus which is next in frequency to the echinococcus has been found in the myocardium but produces no symptoms whatever or only such general symptoms—dropsy, pectoral pain and evidence of hypertrophy—as are not sufficiently characteristic to lead to a diagnosis Trichinosis may result in an acute interstitial myocarditis and parenchymatous degeneration with clinical evidence of circulatory failure in the fourth to the seventh week In the fatal cases however the embryos are not found in the heart muscle. The prolonged hypotension is vasomotor in origin The treatment is prophylactic and symptomatic

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FOREIGN BODIES

Foreign bodies occasionally penetrate the heart from without through injury or reach the heart through the great veins the

bronchi esophagus or stomach Various foreign bodies have been found such as fragments of projectiles needles bullets broken ends of swords files knives tooth picks splinters of wood etc The embolic route is very rare Foreign bodies have wandered through the heart and great vessels They cause little reaction hardly any clinical symptoms and are usually accidental necropsy findings Thrombi more especially the ball thrombi and pedunculated thrombi cannot strictly be included among the foreign bodies

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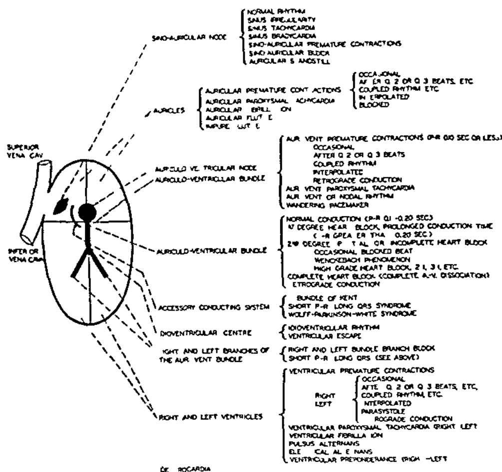


Fig 122—Here is shown a diagram of the heart and its areas of specialized tissue with an outline of the rhythms to which each part may give rise

Functional Disorders of the Heart

CARDIAC ARRHYTHMIAS

Cardiac rhythm connotes the sequence of the heart beats It may be regular or irregular The irregularity may be perpetual as in auricular fibrillation or may disturb the normal sequence occasionally or at regular intervals and the cardiac rate may be rapid or slow The heart with its areas of specialized tissue together with the related rhythms is shown in Fig 122 The normal stimulus initiating the heart beat arises in the sinus node which lies in the right auricle in the region of the opening of the superior vena cava It spreads in a radical fashion over the auricles and induces their contraction and

arriving at the auriculoventricular node which lies at the lower part of the inter auricular septum proceeds rapidly down the auriculoventricular bundle and over the

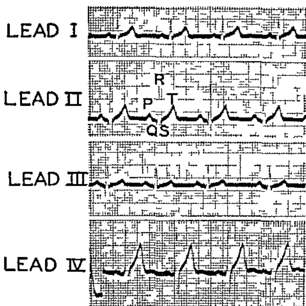


Fig 123—This figure shows the three standard leads and the chest lead of a *normal* electrocardiogram The leads and waves are identified The P waves the major part of the QRS deflections and the T waves are upright in all leads and P R is 0 17 seconds QRS_ 0 06 seconds rate 75 per minute Lead I is derived from the electrodes placed on the right and left arms Lead II from the right arm and left leg and Lead III from the left leg and left arm To obtain chest Lead IV the precordial electrode is placed 1 cm outside the apex beat and the indifferent electrode on the left leg Using Lead III selector of the gal vanometer control box the left leg wire is attached to the precordial electrode and the left arm electrode to the left leg in order to secure upright T waves in normal curves The P R interval measures the time for passage of the excitation wave from the sinus node through the auricles to the auriculoventricular node down the auriculoventricular bundle to the beginning of ventricular activity and normally does not exceed 0 20 seconds The QRS interval represents the time of spread of the excitation wave through the ventricles by way of the special conduction system and is normally not greater than 0 10 seconds The Q T time from the beginning of QRS to the end of T measures ventricular systole The three standard leads of the electrocardiogram obey the laws of the Einthoven equi lateral triangle namely that the amplitudes of any waves of the complexes in Lead II equal the sum of those in Lead I and *Lead III Standardization in all* records unless specifically mentioned is such that one millivolt produced 1 cm deflection of the string Divisions of the ordinates equal 10^{4} volts Divisions of the abscissae equal 0 04 seconds

right and left branches in the ventricular septum simultaneously and finally is distributed by the Purkinje fibers to the ventricular muscle and results in synchronous contraction of the two ventricles

The sinus discharge is usually more rapid than the inherent rate of the auriculoventricular node and the idioventricular center over which it takes precedence as the pacemaker Normally, conduction is forward from auricles to ventricles but occasionally may be retrograde The activity of the sinus node is affected by the vagus and the accelerator nerves Most of the fibers of the right vagus are distributed to the sinus node and most of the fibers of the left vagus to the auriculoventricular node and a few to the bundle The heart beat is the expression of a physiologic mechanism and has no histologic counterpart that can be discovered at present except in heart blocks

The **physiologic properties** of heart muscle concerned with its rhythms are (1) *excitability or contractility* it responds to a stimulus by contracting (2) *refractory period* having contracted a recovery period is necessary before it can respond to the next stimulus (3) *automaticity or rhythmicity* the property of initiating impulses, (4) *conductivity* it conducts an impulse that it receives

Method of Examination—Orderly examination facilitates the clinical recognition of arrhythmias 1 The jugular bulbs and external jugular veins which become dis*tended if the patient lies flat* are observed for pulsations which are magnified by using as a lever a narrow strip of paper bent at a right angle near one end and applied to the moistened skin overlying the vessel The a (auricular contraction) c (ventricular contraction) and v' (ventricular filling) waves can usually be identified by this technic when the heart is beating normally 2 The sequence of beats in the radial pulse is analyzed 3 The rhythm is analyzed on auscultation correlating it with radial and carotid pulses auricular contractions may be heard in complete heart block and in auricular flutter 4 The apex and radial rates are counted simultaneously for one minute to estimate the pulse *deficit* 5 The physician may tap one foot as a metronome to accompany the basic rhythm and then detect deviations from it If careful clinical examinations are made and then checked with electrocardiograms whenever possible a skill is acquired which permits proceeding without them when they are not available Elec

trocardiograms record the electrical activity of the heart accompanying contraction The normal cardiac cycle consists of a P wave indicating auricular activity followed by the QRS complex recording the spread of the excitation wave through the ventricles and in turn by the T wave coinciding with the retreat of electrical activity associated with contraction after which there is an isoelectric pause before the onset of the next P wave (Fig 123)

varies and sinus irregularity is present The rate may wax and wane in a repetitive pattern When the irregularity is respiratory it is easily diagnosed because the rate may increase with inspiration and decrease with expiration (Fig 124B and C) It is a physiologic phenomenon It is most common in children and young individuals It may disappear during rheumatic carditis It may occur after digitalis It may be confused with auricular fibrillation with a slow ven-

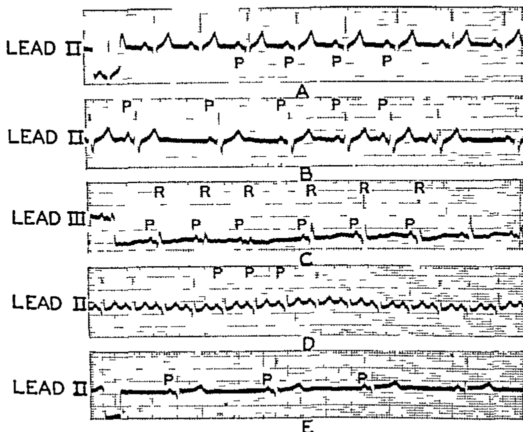


Fig 124—Here are reproduced electrocardiograms showing variations in discharge from the sinus node In A the discharge is regular and the complexes are equally spaced (Lead II) In B there is sinus irregularity (Lead II) and in C there is sinus irregularity with marked respiratory variation in the amplitudes of the QRS complexes (Lead III) D records sinus tachycardia (15 per minute) (Lead III) and E sinus bradycardia (37 per minute) (Lead II) P = auricular complexes R = ventricular complexes

Sinus Node—Normal Rhythm—The heart beat controlled by the sino auricular node is called normal or regular (sinus) rhythm or normal (sinus) mechanism The discharge of impulses may be quite regular (Fig 124A) or may have the following variations

Sinus Irregularity or Sinus Arrhythmia—When the sinus discharge is irregular (Fig 124B and C) the length of the cycle

tricular rate (Fig 129A) however in sinus irregularity there is no pulse deficit and increasing the heart rate with exercise dispels the irregularity but might elicit a pulse deficit in fibrillation The sequence of P QRS T waves in the electrocardiogram is normal but the P P interval varies (Fig 124B and C) In pericardial effusion chronic constrictive pericarditis labored respiration of asthma and in certain normal individuals

there may be *pulsus paradoxus* the *pulse volume decreases in inspiration* instead of *increasing and increases in expiration* instead of decreasing This may be verified when taking the blood pressure

Sinus tachycardia occurs when the discharge of impulses from the sinus node is over 100 per minute The rate may be 200 but the lower ranges above 100 are more common

ETIOLOGY —Sinus tachycardia is normal in a few individuals It may result from depression of vagus activity or from stimulation of the accelerator nerves and may be induced by atropine or by adrenalin It is a physiologic response to exercise eating, excitement and fear It occurs in neurasthenia neurocirculatory asthenia anemia pulmonary tuberculosis hyperthyroidism infections (except typhoid fever) especially rheumatic fever active rheumatic carditis coronary occlusion heart failure and following hemorrhage

PATHOLOGIC PHYSIOLOGY —The normal heart augments its output in response to exercise and increased oxygen consumption by increasing its rate In experiments which eliminate the effects of exercise and metabolism accelerating the heart by atropine increases the cardiac output per minute In cardiac patients tachycardia resulting from atropine does not alter the arterial but increases the venous oxygen saturation The effects of prolonged tachycardia are not known

SYMPTOMS —There may be no symptoms or there may be palpitation or pounding of the heart especially in neurasthenia and hyperthyroidism

DIAGNOSIS —In sinus tachycardia the rate usually accelerates and retards gradually in contrast to the sudden onset and offset in paroxysmal tachycardia In electrocardiograms the normal sequence of P QRS T is observed but the P-P interval is short (Fig 124D)

TREATMENT —The heart rate accelerated by exercise retards on resting as well as when other precipitating factors are alleviated Sedatives may be effective

Sinus bradycardia occurs when the sinus impulses are fewer than 50 per minute

ETIOLOGY —Sinus bradycardia is not unusual in athletes and young adults It occurs during sleep It may be associated with malnutrition jaundice and increased intracranial pressure due to brain tumor, meningitis or intracranial hemorrhage It may result from digitalis or from carotid sinus pressure

PATHOLOGIC PHYSIOLOGY —In sinus bradycardia the cardiac output per minute may decrease *because of the slow rate the stroke* volume however may be increased

SYMPTOMS —There are usually no symptoms

DIAGNOSIS —The diagnosis of sinus bradycardia is not difficult unless the rate is slow enough for confusion with complete heart block It accelerates with exercise If very slow the auriculo ventricular node assumes pacemaking or there may be ventricular escape In electrocardiograms there is normal sequence of P QRS T but the P P interval is long (Fig 124E)

TREATMENT —Sinus bradycardia requires no specific treatment except for the underlying condition which at times may be responsible for it It is rarely necessary to use atropine

Sino-auricular Premature Contractions — It is unusual for the sinus node to initiate premature contractions They cannot be differentiated clinically from other premature beats (p 1116) In electrocardiograms the P waves are similar in form to the normal ones indicating their mutual origin but they occur early and are not followed by a compensatory pause

Sino auricular block sinus pause or arrest occurs when the discharge of impulses from *the sinus node is interrupted* It may be occasional frequent or in a recurrent pattern or there may be longer periods of block

ETIOLOGY —Sino auricular block may result from *increased vagal activity* It may be precipitated by quinidine potassium salts or digitalis When the sinus node is quiescent for a few seconds syncope may result It may follow carotid sinus stimulation *If this tissue is hypersensitive* attacks may be precipitated by sudden turning of the head a tight collar bending forward One carotid sinus is usually more sensitive than the other

PATHOLOGIC PHYSIOLOGY — Occasional sino auricular block does not affect the func

tional capacity of the heart When it is prolonged the cardiac output and the blood pressure fall to zero until the ventricles escape

SYMPTOMS.—Occasional sinus pause is usually without symptoms If there are longer periods of block with asystole Stokes Adams like attacks occur with giddiness or even syncope and convulsions because of cerebral anemia

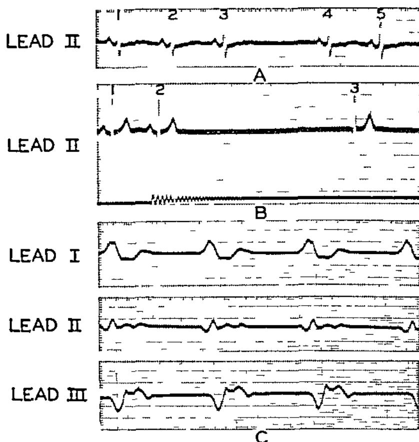


Fig 125—A is reproduced (Lead II) to show sino auricular block The interval from 3 to 4 equals twice the interval from 1 to 2 or equals interval 1 to 3 B shows sinus arrest with cardiac standstill (asystole) for 8 sec resulting from right carotid sinus pressure (Lead II) Ventricular escape occurs at 3 The signal at the bottom indicates the onset of carotid sinus pressure C records three leads showing auricular standstill with idioventricular rhythm and bundle branch block which probably resulted from toxic effect of potassium chloride The patient exhibited normal rhythm before the onset of this rhythm

DIAGNOSIS —Single sino auricular block can occasionally be detected because the pause equals two usual intervals It is to be differentiated from auriculoventricular block When the pause is of longer duration as in carotid sinus hypersensitivity the diagnosis should be suspected because of asystole which can be recognized on auscultation In testing for carotid sinus sensitivity (see p 1119 point 4) pressure may be applied for 5 to 15 seconds asystole may last for 7 to 8 seconds before the ventricles escape (Fig 125B) In electrocardiograms single sino auricular block is recognized by the absence of auricular and ventricular activity and the interval covering the block approximately equals two normal intervals (Fig 125A) and longer periods of sinus arrest may be recorded with ventricular escape (Figs 125B and 137B)

TREATMENT —Occasional sino auricular block requires no specific therapy If it is due to carotid sinus hypersensitivity and associated with symptoms atropine 0 0006 Gm (1/100 gr) three times a day Tr Belladonna 0 6 to 1 0 cc (10 drops) three times a day ephedrine 20–30 mg (1/3 to 1/2 gr) three times a day or luminal 0 015 Gm (1/4

gr) four times a day orally may be used If these measures are ineffective one or both carotid sinuses may be denervated If due to digitalis and infrequent digitalization may be continued if the drug is necessary

Auricular Standstill —In this rhythm the sinus node is quiescent the auricles fail to contract and there is ventricular escape with

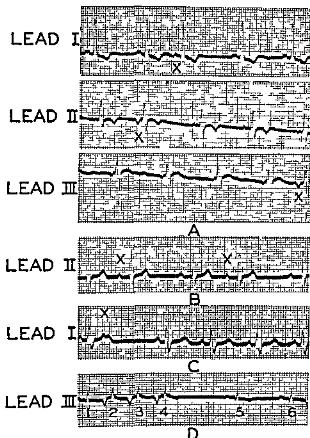


Fig 126—In A are shown the three standard leads in which auricular premature contractions (X) are recorded in each lead In B the auricular premature contractions (X) recur and give rise to coupling In C there is an auricular premature contraction (X) superimposed on the T wave and it occurs so early that it is blocked (ventricles refractory) In D the first complex (1) is normal followed by a run of 3 auricular premature contractions in succession (2 3 4) giving rise to a short run of auricular paroxysmal tachycardia followed by reversion to normal rhythm in the fifth and sixth complexes

idioventricular rhythm It occurs transiently in carotid sinus hypersensitivity As a persistent rhythm only a few instances have been reported Death results if the idioventricular center fails to initiate ventricular contractions Auricular standstill may occur as a toxic effect of potassium salts and quinidine on the sinus node and auriculoventricular system Calcium chloride 0.5 Gm (7½ gr) intravenously or barium chloride 30 to 40 mg (½ to ⅔ gr) orally may increase cardiac irritability In the electrocardiogram P waves are not seen and there is idioventricular rhythm (Fig 125C)

Premature contraction is the best term for an irregularity resulting from contractions which are derived from abnormal stimuli arising in various parts of the heart *Extrasystole* implies an extra feat of the heart, because of the pause following the premature contraction the number of beats per minute is not increased The term extrasystole applies only when the premature contraction is interpolated between two normal beats without disturbing the sequence (p 1139) The terms ectopic' and 'aberrant' imply an unusual place of origin and manner of spread of the excitation wave and would not include sino auricular premature contractions without assuming that they arose from a different part of the sinus node *Dropped* beats are seen in heart block. *Intermittent* pulse is vague The occurrence and volume of the pulse accompanying a premature contraction depend on its time in the cardiac cycle Premature contractions may arise from areas of increased irritability The mechanism might be the reentry of a previous excitation wave by way of an area of muscle which was refractory when the impulse first approached it but had recovered when the same impulse came to it slightly later by another route

Auricular Rhythms —*Auricular premature contractions* are occasioned by abnormal stimuli arising in one of the auricles which causes them to contract prematurely and also passing down the auriculoventricular system initiates ventricular contraction Auricular premature contractions may occur occasionally (Fig 126A), several in a sequence (Fig 126D) or according to a pattern (Fig 126B)

Etiology —Auricular premature contractions occur more frequently in younger than in older individuals and are not as common as ventricular ones They may not be significant They may be associated with active rheumatic fever and other infections especially pneumonia they occur in organic heart disease especially mitral stenosis coronary artery disease chronic constrictive pericarditis during pericardiectomy and fol

lowing coronary occlusion They are frequent during periods of stress and may result from coffee alcohol tobacco

Pathologic Physiology —Occasional auricular premature contractions do not disturb the circulation significantly when they cause coupling the cardiac output decreases

Symptoms —Patients may be unaware of the irregularity They may complain of palpitation the pause after the premature contraction the prematurity the quick beat the forceful beat following the premature one the heart turning over fluttering in the heart fulness of the neck veins a catch in the throat and cough Their persistency may cause fatigue

Diagnosis —Auricular premature contractions are detected by their prematurity both on auscultation of the heart and on palpation of the pulse They cannot always be differentiated from ventricular or auriculoventricular ones The dominant rhythm is disturbed if the foot taps synchronously with the heart beat it will not automatically get in step after the premature contraction The sounds accompanying the premature beat approach the usual ones The premature complex in the electrocardiogram consists of a P wave of different contour a P R time exceeding 0 10 seconds and a QRS complex of supraventricular form which may differ from the usual ones (Fig 126A)

Prognosis —Their occurrence may be fleeting They may occur for years without significance They may precede the onset of auricular fibrillation in mitral stenosis and are common in patients subject to auricular paroxysmal tachycardia

Treatment —Treatment is usually not necessary for they may disappear when the precipitating factors are alleviated Attention should not be directed to them because it may induce symptoms Patients are reassured Cigarettes coffee and alcohol are eliminated when implicated When treatment is required triple bromides 1 0 Gm (15 gr) three times or twice a day orally may dissipate them and are usually more effective than luminal 0 015 Gm (¼ gr) three times a day The patient is warned of drowsiness and drug rash If the irregularity disappears the drug is decreased and frequently may be discontinued without recurrence If sedation fails digitalis in full therapeutic amounts (see auricular fibrillation) is the most effective drug Quinidine 0 2 Gm (3 gr) three times a day (see auricular fibrillation) is less effective than in the relief of ventricular ones Occasionally potassium chloride or phosphate 2 Gm (30 gr) three times a day by mouth is beneficial Auricular standstill as a toxic effect of potassium must be kept in mind Papaverine 0 06 Gm (1 to 5 gr) three to four times a day at three to four hour intervals may abolish them

Blocked Auricular Premature Contractions —Occasionally an auricular premature contraction may be blocked if it arises early in diastole because the ventricles are still refractory This irregularity is detected in electrocardiograms (Fig 126C)

Auricular paroxysmal tachycardia is a rapid *regular* beating of the heart controlled by stimuli arising from a focus in the auricles and characterized by sudden onset and sudden offset It may be considered a succession of auricular premature contractions It may persist for a few beats only or for days The rate is usually rapid around 150 per minute but is frequently up to 250 per minute and very rarely less than 100

Etiology —It is more common in younger individuals than the ventricular type There may be a single attack or recurrences at rare or frequent intervals It occurs without organic heart disease It may be precipitated by excessive alcohol intake cigarettes gastro intestinal upsets or sudden change in position It may be associated with acute infections acute rheumatic fever being the most common and pneumonia next It occurs in mitral stenosis thyrotoxicosis during precardiectomy acute coronary occlusion during pregnancy and in patients with Wolff Parkinson White syndrome

Pathologic Physiology —During auricular paroxysmal tachycardia the cardiac output per minute decreases and the amount per beat from the normal average of 60 cc to a few cubic centimeters only The heart dilates the circulation time increases The vital capacity decreases The oxygen saturation of both the arterial and venous blood decreases If prolonged heart failure may occur especially in mitral stenosis *Transient* electrocardiographic changes have been re-

ported, presumably due to the anoxemia of heart muscle from decreased coronary flow There may be cyanosis A few rales at the lung bases, fall in blood pressure fever and leukocytosis are not unusual

SYMPTOMS —Patients are usually aware of the disturbed rhythm They complain of fluttering of the heart that started suddenly rapidity of the heart, palpitation throbbing or fullness of the neck vessels Common complaints are weakness faintness shortness of breath and sensation of the heart stretching There may be apprehension and nervousness Cardiac distress may simulate the symptoms of coronary occlusion Nausea and vomiting a sense of fulness dizziness fainting and loss of consciousness may be experienced When the blood pressure falls the picture may be one of shock

DIAGNOSIS —*Paroxysmal tachycardia* may be diagnosed from the *history* of sudden onset and offset but the type cannot be decided unless the patient is examined during an attack since auricular nodal and ventricular tachycardia and auricular fibrillation and flutter may be paroxysmal Awareness of an irregularity suggests fibrillation The rapidity and regularity are apparent both on auscultation and on tapping the rhythm with one foot The rate is not influenced by respiration or exercise but may change in several hours Pulsations in the jugular veins are rapid and "c" waves may be identified The pulse is rapid of small volume and rarely alternating If carotid sinus pressure or ocular pressure terminates the attack it is likely to be supraventricular In electrocardiograms P waves of abnormal form are detected with P R exceeding 0 10 second and usually a supraventricular form of the QRS complex (Figs 127A B and C) There may be 2 1 block.

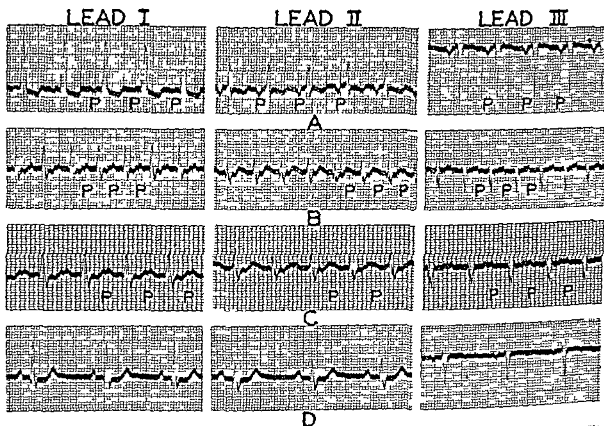


Fig 127—In A are shown the three leads recording auricular paroxysmal tachycardia rate 107 per minute (P = P waves) In B is shown another example of auricular paroxysmal tachycardia rate 16? per minute In C is shown the same paroxysm with the speed of the electrocardiographic film increased to spread out the complexes and aid in identifying the P waves D shows the electrocardiogram after reversion to normal rhythm (rate 61 per minute) from the auricular paroxysmal tachycardia recorded in B and C

PROGNOSIS —Auricular paroxysmal tachycardia frequently indicates heart disease but may recur for many years without other abnormalities there may be a single attack

Its occurrence increases the hazards of the underlying disease

TREATMENT—The first problem is to stop the attack and the second to prevent recurrence The patient should be reassured and kept in bed especially when mechanical stimuli or drugs are used If possible electrocardiograms should be taken before and during attempts to stop the paroxysm Patients may report measures that have stopped previous attacks

Attacks are usually terminated by inducing vagal or parasympathetic effects (1) Holding the breath as long as possible or expiring against the closed glottis (*Valsalva*) or inspiring after closing the glottis (Muller) (2) bending forward or lying down with feet in the air or (3) mechanical induction of *nausea* may terminate the attack. (4) *Carotid sinus pressure* is frequently effective Effects which were formerly attributed to vagal pressure were due to carotid sinus pressure The patient should be recumbent during this maneuver and atropine 0 0006 Gm ($\frac{1}{100}$ gr) for intravenous use or adrenalin 1 cc. (15 minims) 1 1000 (hypodermic) should be ready for immediate injection should asystole persist too long The right and then the left carotid sinus is pressed after which both may be stimulated Pressure for five to ten seconds is effective in suitable cases The carotid bulb which is easily identified in the bifurcation of the common carotid is compressed against the cervical spine This procedure should not be taught the patient Auscultation warns of asystole.

(5) In the long run the most effective drug is *digitalis* With the patient in bed digitalization is carried out rapidly in twenty four hours (p 1122) 1 8 Gm (27 gr) is the average digitalizing amount of the powdered leaf (U.S.P XII) if given orally in twenty four hours and the subject has had no digitalis within three weeks If reversion does not occur during the twenty four hours of digitalization as is common (Fig 127B C D) 0 2 Gm (3 gr) three times or twice a day are given the next day If the clinical strength of the preparation is not known smaller amounts are used 1.5 Gm (22½ gr) in twenty four hours It is not necessary to give the drug intramuscularly or intravenously (6) Acetyl beta methylcholine (*mecholyl*) subcutaneously is frequently effective 10–20 mg ($\frac{1}{6}$ to $\frac{1}{3}$ gr) are given subcutaneously to those ten to twenty years of age 30–40–50 mg (½ to ¾ gr) to those more than fifty years 30 mg (½ gr) being the average dose It should not be given without having atropine 0 0006 Gm ($\frac{1}{100}$ gr) ready for intravenous use if asystole is prolonged or if the side effects are marked Gentle massage of the site of injection enhances the effect The patient should be lying down in case fainting or asystole occurs Because the drug induces increased bronchial secretions profuse expectoration asthmatic breathing due to bronchospasm urticaria and involuntary stools it should not be used without preparations beforehand to meet them History of such allergic manifestations as asthma and hay fever or of sensitivity to sea food and strawberries are contraindications to its use Mecholyl results in auriculoventricular block long periods of ventricular quiescence or auricular standstill before reversion to normal rhythm occurs The synchronous use of mecholyl and carotid sinus pressure may be effective (7) If these measures fail *quinidine sulfate* orally is occasionally effective (p 1123) The use of quinidine hydrochloride 0.2 Gm to 0.3 Gm (3–5 gr) intravenously is limited to those instances when other measures have repeatedly failed and the persistence of the rhythm is deleterious When electrocardiograms are not available and the diagnosis is not established and drug treatment has to be instituted it is better to use quinidine than digitalis because of the danger of digitalis inducing ventricular fibrillation if the rhythm should be ventricular paroxysmal tachycardia. (8) Unilateral ocular pressure is very painful and is too rarely effective to use routinely (9) Apomorphine 5 mg ($\frac{1}{12}$ gr) hypodermically or syrup of ipecac 4 to 8 cc (1 to 2 drachms) by mouth which may be repeated are used to induce vomiting during which the attack may stop They are not resorted to often (10) Occasionally triple bromide 1 0 Gm (15 gr) three times a day by mouth or morphine 16 mg (¼ gr) hypodermically may terminate the attack although the latter is not recommended because paroxysmal tachycardia recurs.

Prevention of attacks is more difficult

Elimination of the precipitating factors may be sufficient if attacks occur at wide intervals If they occur at weekly or ten day intervals the most effective therapy is full digitalization followed by ration doses In other instances quinidine 0 2 Gm (3 gr) once or twice daily is effective although it is usually not desirable to give it over long periods Electrocardiograms are taken occasionally to detect prolongation of P R and of QRS conduction

Auricular Fibrillation—Auricular fibrillation is an irregularity in which the sinus node no longer controls the rhythm of the heart It is characterized by absence of coordinated auricular contraction tumultuous rapid twitching of auricular muscle fibers and total irregularity of the ventricular beats Instead of the usual origin and spread of the sinus stimulus an excitation wave courses continuously through the auricular muscle over a circular pathway about the opening of the great veins The great speed of the excitation wave 400–600 occurring per minute, and the continual variation in the length and course of the pathway account for the irregularity in the auricular action in the electrocardiogram Not all of these stimuli traverse the auriculoventricular bundle because of its refractoriness nor can the ventricles respond to all arriving there because of their refractoriness consequently the ventricular rate before digitalization is usually rapid and irregular (Fig 128A), but slower than auricular activity

Etiology—Auricular fibrillation is the most common rhythm requiring therapy Though commonly associated with organic heart disease, both transient and permanent types occur without it It may follow excessive intake of alcohol oversmoking, over eating food poisoning surgical operations It occurs transiently in acute rheumatic fever, pneumonia, particularly in the older decades coronary occlusion and pulmonary infarction It is frequently associated with chronic rheumatic heart disease especially mitral stenosis, less frequently with the arteriosclerotic and hypertensive types infrequently with luetic and congenital forms extremely infrequently with subacute bacterial endocarditis occasionally with diphtheria and chronic constrictive pericarditis and transiently during pericardiectomy After mitral stenosis its most frequent occurrence is in thyrotoxicosis frequently reverting to normal rhythm after operation It has been observed in a child three and one half years of age but is more common in later years

Pathologic Physiology—*On observation of the fibrillating heart the auricles* appear dilated and coordinated contraction is replaced by quivering of the auricular surfaces while the ventricles beat at totally irregular intervals There is decrease in car

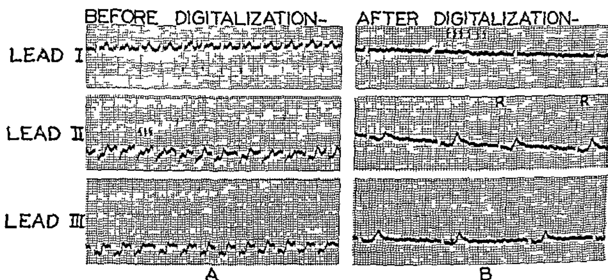


Fig 128—In A are recorded three leads showing auricular fibrillation before digitalization showing the irregular fibrillation waves (fff) the rapid ventricular complexes (R R) (ventricular rate approximately 175 per minute) which occur irregularly B shows the effect of digitalization in this same patient the slower ventricular rate (59 per minute) and the change in T waves

diac output per minute and dilatation of the heart irrespective of whether or not heart disease is present and the state of compensation Due probably to the slow circulation rate permitting a longer time for oxygenation of the blood in the lungs there is *increase* in the arterial oxygen saturation until heart failure supervenes and decrease in venous oxygen saturation

During tachycardia there is little blood in the ventricles when systole occurs so that contraction fails either to open the aortic valve or to expel enough blood to form a radial pulse accounting for the *pulse deficit* at the next systole there will be a greater accumulation of blood so that the radial pulse is barely palpable or will be larger accounting for variations in pulse volume The pulse deficit represents expenditure of cardiac energy which is wasted The blood pressure changes from beat to beat Fibrillation may be accompanied by fever due to decreased elimination of heat with the retardation of the blood flow Leukocytosis may occur The onset of fibrillation may be beneficial in some patients exhibiting mitral stenosis because the ventricular rate can be satisfactorily controlled

The presystolic murmur of mitral stenosis is due to auricular contraction If the presystolic murmur and thrill have been present during normal rhythm the timing of the murmur and thrill change with the onset of fibrillation so that they appear early in diastole or in mid diastole when the intra auricular pressure is greatest because of the absence of orderly contraction of the auricles to promote ventricular filling Occasionally during tachycardia the sequence of sounds makes a mid diastolic murmur appear presystolic this discrepancy disappears when the rate is retarded

Symptoms —Patients may be unaware of the rhythm or of the date of onset Paroxysmal fibrillation is more likely to give symptoms Patients may be unable to separate the symptoms of heart disease from those of arrhythmia They may complain of irregular beating of the heart described as fluttering palpitation skipping pounding or of fulness and fluttering of the neck veins In both the chronic and paroxysmal forms apprehension and irritability may be present for a short time after onset as well as dizziness or faintness Exertion may provoke dyspnea and the persistence of tachycardia may precipitate heart failure Angina pectoris is uncommon

Diagnosis —The clinical diagnosis is not difficult and is easier if the ventricular rate is rapid or before digitalization On auscultation the rhythm is usually totally irregular If the foot is tapped synchronously with contractions a regular sequence cannot be detected The pulse is usually slower and is irregular and of variable volume Simultaneous auscultation of the heart and palpation of the pulse reveals the magnitude of the *pulse deficit*. The ventricular rate and pulse deficit increase with moderate exercise while the irregularity due to premature contractions is likely to disappear The ventricular rate may be 180 but usually is 130–160 and occasionally is as low as 70 or 80 even without digitalis Carotid sinus pressure retards the ventricles transiently With slower ventricular rates or after digitalis the irregularity may be less marked and the pulse deficit small Occasionally the ventricular beats are regularly spaced (Fig 129A) and clinical recognition may be impossible unless exercise increases the rate and elicits irregularity With a slow rate it may be confused with sinus irregularity or frequent premature contractions The electrocardiogram is characterized by absence of definite P waves the presence of fibrillation waves and irregular sequence of the QRS complexes (Fig 128)

Prognosis Complications and Course —When the ventricular rate is slow patients maintain an adequate circulation for years without progressive cardiac enlargement or failure Others carry on satisfactorily when the rate is controlled The paroxysmal form may lead to no apparent harm in the course of years Chronic fibrillation does not in itself carry serious prognosis but as a complication of heart disease it comes on usually toward the end of the natural history of the disease Its onset may precipitate failure especially in organic heart disease or pneumonia Sluggishness of blood flow in the auricular appendages plus lack of coordinated contractions promote formation of mural thrombi and their dispersal in the blood stream Infarction of the brain spleen kidneys and occlusion of peripheral arteries

may occur Pulmonary infarcts result from thrombi from the right auricle or by paradoxical embolism (congenital communication) from the left side of the heart Patients tolerate surgical procedures when adequately digitalized

TREATMENT —If the ventricular rate is slow if it accelerates only moderately on exercise, and if the patient is without symptoms *special treatment is not indicated* although the use of quinidine should be considered If the rate is rapid especially if the patient has heart disease, rest in bed is indicated if possible until it is retarded and is required if there is failure If the patient is in bed and digitalis has not been given in three weeks *digitalization* may be undertaken rapidly by giving in twenty four hours by mouth a total of 1 8 Gm (27 gr) of the powdered leaf (U S.P XII) Experience *has shown that this is the average* amount which if given in twenty four hours *to patients with auricular fibrillation and* rapid ventricular rates will retard the rate to 70 or 80 per minute without nausea and vomiting If digitalization is accomplished in twenty four hours excretion during this time may be neglected The 1 8 Gm (27 gr) may be distributed as follows 0 8 Gm (12 gr) as the first dose 0 5 Gm (7½ gr) four to five hours later 0 3 Gm (5 gr) four to five hours after this and 0 2 Gm (3 gr) four to five hours later still (Fig 128A B) If the clinical strength of the preparation is not known, smaller amounts are used Stand*ardization of digitalis by the cat method* (U S P XII) aims to supply digitalis preparations of *uniform potency The amount of* such uniform preparations required to induce certain effects *in* patients *must* then be ascertained Experience has shown that the clinical strength of digitalis can be gauged by its effect in slowing the ventricular rate in auricular fibrillation The digitalizating amount of the preparation which is available may be ascertained therefore by establishing the amount required to slow the rapid ventricular rate in auricular fibrillation to 70 or 80 per minute If the patient is partially digitalized 0 2 to 0 3 Gm (3 to 4 gr) twice or three times a day may be given Cardiac rate and pulse deficit are counted frequently during digitalization Successive doses are withheld if nausea or vomiting occur or if the rate falls below 60 to 70 or ventricular premature contractions appear Digitalization should be accomplished without toxicity Nausea vomiting and ventricular premature contractions however may be due *to heart failure and* may disappear on digitalization The ven*tricular rate is a reliable clinical guide to* digitalization in fibrillation and the aim *should* be to reduce it to around 70 per minute (Fig 128A B) Slightly more or slightly less than 1 8 (27 gr), which is the average amount may be necessary Having reduced the rate it is maintained around this level by ration amounts The average ration is 0 2 Gm (3 gr) a day using the rate as a guide, 0 1 Gm (1½ gr) alternating with 0 2 Gm (3 gr) or 0 2 Gm (3 gr) alternating with 0 3 Gm (5 gr) daily and occasionally more may be required Experience has *shown that a resting apical rate of* 60 to 70 is satisfactory and allows for moderate increase with exercise

If the patient is nauseated and vomits digitalization may be accomplished by giving the drug by rectum as microenemata in the same dosage as by mouth It is rarely necessary to use digitalis intravenously or intramuscularly It should be established that the patient has not had digitalis for three weeks before giving it intravenously If there is urgency strophanthin K (0 25 mg) or digitoxin 0 4 mg q 4 h for three doses may be given intravenously or digifoline intramuscularly There has been however *insufficient experience under varied* circumstances with the highly purified digi*talis glucosides* to warrant their routine use although they hold promise

If the patient remains ambulatory digitalization is accomplished more slowly Knowing the average *amount of the* preparation required for digitalization in twenty four hours (1 8 Gm [27 gr]) *and the daily* maintenance amount (0 2 Gm [3 gr] alternating with 0 1 Gm [1½ gr]) *and the number of* days it is appropriate to take for digitalization the total amount *required for digitaliza*tion in this number of days is calculated If digitalization is spread over one week the regime may be as follows 1 8 Gm (27 gr) required to digitalize +0 9 Gm (15 gr) to maintain digitalization (0 1 Gm [1½ gr] alternating with 0 2 Gm [3 gr] *for 6 days*)

amounts to 2.7 Gm (42 gr) to be given during the week which may be spread somewhat as follows (Table 1)

TABLE 1 DIGITALIS ADMINISTRATION FOR ONE WEEK

Day	*Digitalis (U.S.P. XII)* AM	PM	*Amount for the day*	*Total to date*
1	0.3 Gm (5 gr)	+0.3 Gm (5 gr)	=0.6 Gm (10 gr)	0.6 Gm. (10 gr)
2	0.3 Gm (5 gr)	+0.2 Gm (3 gr)	=0.5 Gm (8 gr)	1.1 Gm (18 gr)
3	0.2 Gm (3 gr)	+0.2 Gm (3 gr)	=0.4 Gm (6 gr)	1.5 Gm (24 gr)
4	0.2 Gm (3 gr)	+0.1 Gm (1½ gr)	=0.3 Gm (4½ gr)	1.8 Gm (28½ gr)
5	0.2 Gm (3 gr)	+0.1 Gm (1½ gr)	=0.3 Gm (4½ gr)	2.1 Gm (33 gr)
6	0.2 Gm (3 gr)	+0.1 Gm (1½ gr)	=0.3 Gm (4½ gr)	2.4 Gm (37½ gr)
7	0.2 Gm. (3 gr)	+0.1 Gm (1½ gr)	=0.3 Gm (4½ gr)	2.7 Gm (42 gr)

Toxic symptoms are not expected after the first doses but would be more likely to occur toward the end of the week accordingly the last doses are smaller and the patient warned of toxic symptoms If the clinical potency of the preparation is not known smaller amounts than those listed above are recommended Digitalization by 0.2 to 0.3 Gm (3 to 5 gr) daily takes too long to attain an adequate effect Occasionally in terminal heart disease digitalis fails to reduce the rate or sufficient amounts can not be given without inducing ventricular premature contractions If there is heart failure digitalization commonly results in diuresis which may be sufficient to restore compensation

The reversion of *chronic* fibrillation to normal rhythm with *quinidine* is now undertaken infrequently Reversion should not be attempted (1) if fibrillation has been present for a long time because mural thrombi may be dislodged when the auricles begin contracting regularly (2) if the heart is large (3) during heart failure—compensation should be restored first (4) if failure has been of long duration because the formation of thrombi may have been encouraged (5) without taking into consideration that some patients feel better and the heart rate is more easily controlled during fibrillation. During attempts at restoration the patient should be in bed The ventricular rate is first reduced with digitalis and compensation is restored Digitalis is then discontinued and test made for quinine idiosyncrasy with two doses of quinidine 0.2 Gm (3 gr) at two hour intervals The drug may then be given as follows 0.4 Gm (6 gr) four times a day at four hour intervals the first day normal rhythm may recur at any time If fibrillation persists 0.4 Gm (6 gr) quinidine is given five times a day the second day and 0.4 Gm (6 gr) six times a day the third day If reversion has not occurred larger amounts should not be given at this time but digitalis is resumed and the ventricular rate reduced again If reversion is urgently desired a second attempt may be made attention being given to the occurrence of ventricular premature contractions If normal rhythm is restored maintenance doses 0.2 Gm (3 gr) twice a day are given for a week longer If normal rhythm is restored once but fibrillation recurs while quinidine is being given further attempts are not recommended If it recurs after being discontinued another attempt may be made It is not advisable to use quinidine daily over long periods to prevent recurrence

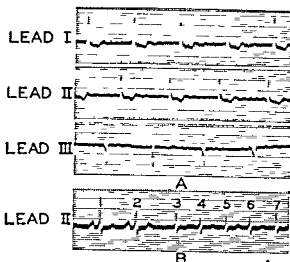


Fig 129 —In A is shown auricular fibrillation in which the ventricular sequences are regularly spaced, ventricular rate 60 per minute In B is shown the transition from normal rhythm (88 per minute) to auricular fibrillation (ventricular rate 125 per minute) Complexes 1 and 2 are normal rhythm and 3 to 7 inclusive auricular fibrillation

Paroxysmal Auricular Fibrillation—

Treatment —If paroxysms are infrequent and brief in an otherwise well subject *specific treatment is not required* beyond avoidance of precipitating factors (Fig 129B) If however the attack has persisted *for several hours or days* if tachycardia prevails if the patient is uncomfortable or if signs of failure are apparent treatment is indicated The patient should be in bed and the ventricular rate reduced with digitalis There is no evidence clinically that digitalis fixes the rhythm and prevents reversion to normal since (1) paroxysmal fibrillation may revert to normal rhythm on digitalization (2) maintenance amounts of digitalis may prevent recurrent fibrillation and (3) *normal rhythm recurs while digitalis is being* given after thyroidectomy If normal rhythm is not restored during preliminary digitalization and if the signs of failure have not been present or have disappeared quinidine may be given (p 1123) If the patient has been treated effectively with quinidine and has no idiosyncrasy instructions may be given about taking the drug on recurrence Ration doses of quinidine are usually not given daily over months or years controlling the ventricular rate with digitalis is more satisfactory Recurrent fibrillation is occasionally prevented by digitalization followed by maintenance doses when quinidine has been ineffectual In acute rheumatic fever it is transient and usually does not require therapy In pneumonia or coronary occlusion prompt slowing of the ventricular rate is necessary the use of quinidine is then considered Occasionally following quinidine fibrillation changes to flutter which persists in spite of large amounts of quinidine or digitalis

The benefits of digitalis are more dramatic in auricular fibrillation than in normal rhythm because of marked slowing of the ventricular rate Digitalis exerts certain other effects on the heart which can be recorded in *patients* 1 An effect on heart muscle is observed objectively in changes in the form and amplitude of T waves of the electrocardiogram (Fig 128A B) This effect however cannot be interpreted in terms of benefit or degree of digitalization 2 Digitalis increases the auriculoventricular block and in adequate dosage prevents most of the fibrillation impulses from passing to the ventricles those passing relatively infrequently find the ventricles containing more blood The ventricular rate is retarded (Fig 128A B) and the pulse deficit is decreased or abolished The blocking effect of digitalis can be pushed to complete heart block Atropine abolishes the vagal effects so that the ventricular rate and pulse deficit increase 3 Digitalis decreases the size of the dilated, fibrillating heart and increases its volume output The failing and the digitalized heart as well as the normal heart appear to obey Starling s law of the heart 4 The extent of ventricular contraction is also increased in roentgenkymograms These effects contribute toward increase in cardiac output per minute and per beat decrease of the circulation time toward normal and fall in venous pressure, if it has been elevated When normal rhythm is restored spontaneously or by quinidine still further increase in cardiac output may occur with other appropriate changes

Quinidine brings about restoration of normal rhythm in fibrillation by increasing the refractory period of auricular muscle As the excitation wave moving in its circuit reaches a certain point it finds that tissue still refractory and unable to transmit it the circus ends and the sinus node assumes control Quinidine also slows the speed of conduction of the impulse and thereby tends to perpetuate the circus motion accordingly when the effect on the refractory period is greater than its contrary effect on conduction normal rhythm supervenes

Quinidine is to be discontinued should there occur ringing in the ears deafness diarrhea nausea vomiting rash fever interventricular heart block ventricular premature contractions rapid regular rhythm or episodes of irregular rhythm suggesting ventricular fibrillation Cerebral accidents or death occurring during quinidine therapy are in some instances due to embolism associated with dislodgment of mural thrombi on restoration of coordinated contraction of the auricles Other instances of *death have* been attributed to cardiac standstill resulting from depression of both the sinus and auriculoventricular nodes *leaving no center* available for pacemaking when the auricles stop fibrillating

When it occurs in *hyperthyroidism* the

ventricular rate is reduced with digitalis Larger than the average amounts may be required to attain adequate slowing Maintenance doses are continued during treatment with iodine and after thyroidectomy In most instances a few days to many weeks after operation the rhythm reverts to normal spontaneously When this occurs digitalis is discontinued if heart failure does not require its continued use If normal rhythm has not recurred after an adequate postoperative period the use of quinidine is considered

Auricular flutter is a rhythm in which the auricles contract regularly at a rate of 200-360 or more per minute and in which the ventricles contract in response to some of these stimuli Flutter is due to the passage of an excitation wave in a circus motion about the opening of the great veins in the right auricle The passage is over a constant pathway and only one impulse is given off from the circumference of the circular pathway with each circuit the auricular impulses occur *regularly* the rate ranging between 200 and 400 per minute but commonly around 320 (Fig 130) which is slower than in fibrillation These impulses spread through the auricular muscle down the auriculoventricular node and bundle to the ventricles but are so rapid that the conducting system cannot readily transmit nor the ventricles respond to so many and auriculoventricular block usually develops The ventricular rate is usually regular and slower than the auricular rate and usually has a constant ratio to it two auricular contractions to one ventricular designated 2 1 auricular flutter is common before treatment (Fig 130) A 1 1 ratio is occasionally observed The most frequent ventricular rate is 150 to 165 per minute Ratios of 3 1 4 1 or 5 1 occur after digitalization (Fig 131B and C) and occasionally before treatment If the ratio fluctuates the ventricular sequence is irregular (Fig 131A) Auricular flutter is more commonly paroxysmal than chronic It may be transient (Fig 131E) but usually persists for hours days or weeks and rarely for many years

ETIOLOGY—Auricular flutter is more commonly associated with heart disease than not It occurs in chronic rheumatic heart disease especially when mitral stenosis is present in hyperthyroidism pneumonia active rheumatic infection hypertensive and arteriosclerotic heart diseases coronary occlusion, and less rarely in congenital heart disease It is far less common than fibrillation and occurs more frequently in the older than in the younger age group It has been reported during pericardiectomy

PATHOLOGIC PHYSIOLOGY—When there is tachycardia as in 2 1 block the cardiac output per minute is markedly decreased so

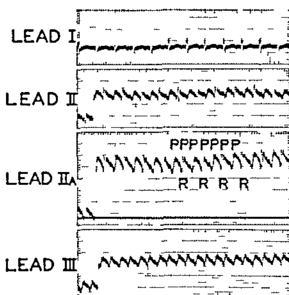


Fig 130—Here are shown the three standard leads recording 2 1 auricular flutter (ventricular rate 187 auricular rate 374) The flutter waves are poorly seen in Lead I but are easily identified in Leads II and III (PPP) of which there are two to one ventricular complex (RRR) In Lead IIA the galvanometer string was standardized for 2 cm instead of 1 cm in order to magnify the flutter waves

that the stroke volume may fall to 13 cc. per beat (normal 60 cc) together with prolongation of the arm to tongue circulation time and cardiac dilatation Rise in venous pressure may be recorded Reversion to normal rhythm is accompanied by restoration of these functions toward normal levels When the ventricular rate is moderately slow the cardiac output may be normal

SYMPTOMS—The patient may complain of rapid heart beat or palpitation which may be described as a fluttering sensation Heart failure may be precipitated or aggravated by its onset Rarely its onset may

be accompanied by syncope due to cerebral anemia and by sweating apprehension and fall in blood pressure

DIAGNOSIS —The ventricular rate is usu

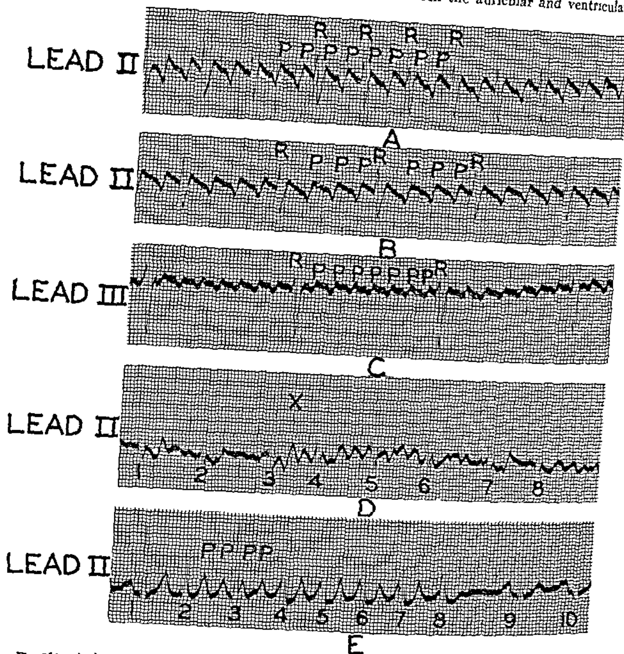


Fig 131 —A shows auricular flutter with the *ratio of auricular* waves (PPP) to ventricular ones (*RRR*) changing from 2 1 to 3 1 (ventricular rate 110 *auricular rate 240*) B 4 1 auricular flutter is recorded (ventricu lar rate 57 auricular rate 228) and in C *the ratio is* 7 1 (ventricular rate 42 auricular rate 294) In D is shown auricular fibrillation 1-2-3 changing *at* Y *to* impure flutter for 4-5-6 and then auricular fibrillation again *for* 7 and 8 In E the first *complex 1 is normal* rhythm followed by 7 complexes (2 to 8) of auricular flutter (PP) in which the position of the ventricular contraction changes and is then followed by reversion to normal rhythm *for complexes 9 and 10*

ally rapid 150 to 160 per *minute* and is not influenced by exercise or holding the breath Block is increased transiently by carotid sinus pressure If block varies the ventricular sequence is irregular When audible, approximately 300 auricular con tractions may be counted per minute and a ratio between the auricular and ventricular rates is detected Occasionally rapid auricu lar waves and *slower larger* ventricular waves are identified in the jugular pulse During 4 1 block when the ventricular *rate*

is around 75 per minute the rhythm may escape recognition The detection of regularly spaced flutter waves in the electrocardiogram establishes the diagnosis (Figs 130 131A B C and E) The auricular rate is greater than in auricular paroxysmal tachycardia but the differentiation is difficult if there is 1 1 ratio

Impure flutter is intermediate between fibrillation and flutter (Fig 131D) Clinically it resembles fibrillation in irregularity of the ventricular sequence but in the electrocardiogram there is a fairly but not absolutely regular spacing of flutter waves at a faster rate than definite flutter interspersed with runs of fibrillation waves

Prognosis—Auricular flutter is usually associated with heart disease It is commonly of short duration if treated but may be chronic

Treatment—Treatment is directed to restoration of normal rhythm The patient should be in bed Digitalis is the most effective drug If the clinical strength of the preparation is known and the ventricular rate is rapid digitalization may be accomplished in twenty four hours by giving 1 8 Gm (27 gr) the average amount in this time (p 1122) As it becomes effective the ventricular rate falls as block increases to 3 1 or 4 1 and may reach 75 per minute during the day Reversion may occur during the first twenty four hours On the other hand if the rate has not retarded sufficiently 0 3 Gm (5 gr) twice during the second day may be required Maintenance doses are given when satisfactory slowing results nausea and vomiting being avoided During this time the rhythm may become normal When the ventricular sequence is irregular it may be due to changing block or to the onset of fibrillation After the onset of fibrillation normal rhythm may follow It may be restored directly from flutter or often there is an intervening period of fibrillation It is not necessary to discontinue digitalis at the onset of fibrillation to insure reversion to normal rhythm

After restoration of normal rhythm digitalis is discontinued unless it is required because of heart failure If normal rhythm is not occasioned by digitalis or if the rhythm has changed to fibrillation which persists without giving way to normal rhythm quinidine sulfate may be used orally digitalis being continued if necessary to keep the ventricular rate slow Fibrillation is more satisfactory as a chronic irregularity than flutter because the ventricular rate is more easily controlled If quinidine is effective maintenance amounts are given for a few days Occasionally, these measures are not successful it may be impossible even to retard the ventricles Recurrent flutter may be prevented by digitalization followed by ration doses If ration doses of quinidine are used for this purpose which is not recommended toxic effects should be foreseen This drug should not be used intravenously unless there is urgency

The use of digitalis to restore normal rhythm is based on its vagal effects Vagal stimulation by the drug shortens the refractory period of auricular muscle and increases the transmission rate This action tends to maintain the gap in the circus shortens the time to make a circuit and the auricular rate increases The direct action of the drug on the auricular muscle on the other hand lengthens its refractory period and slows conduction which tends to close the gap and slow the auricular rate Although the vagal and direct effects are opposite the vagal effect overrides the direct action and converts flutter to fibrillation from which normal rhythm may follow The action of quinidine effective in breaking up the circus motion is the same as in fibrillation it fails when the effect on conduction over balances that on the refractory period

Auriculoventricular Tissue—*Auriculoventricular Nodal or Junctional Premature Contractions*—If an abnormal stimulus arises in the auriculoventricular node or bundle a premature contraction results In a large series of electrocardiograms they are frequently encountered They may occur occasionally or in a pattern

Etiology—Nodal premature contractions occur in normal as well as in diseased hearts especially during active rheumatic carditis and coronary occlusion

Pathologic Physiology—Occasional auriculoventricular premature contractions do not embarrass the circulation appreciably but when frequent may decrease the cardiac output

Symptoms—If infrequent they give rise

to no symptoms There may be symptoms similar to those associated with auricular premature contractions

DIAGNOSIS —They cannot be differentiated clinically from auricular premature contractions The pause after the premature beat *is relatively short The diagnosis is* electrocardiographic The impulse arising in the auriculoventricular tissue passes back

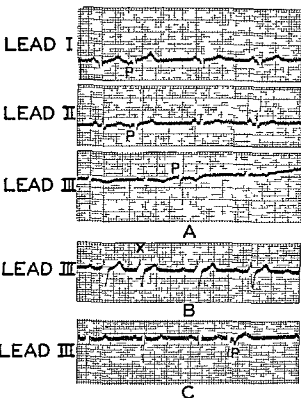


Fig 132 —A records the three standard leads of the electrocardiogram *in which one auriculoventricular premature* contraction (P) arising high in the tissue is recorded in each lead so that the P wave is in front of the QRS complex and the P R time of them 0 08 to 0 09 seconds In B the auriculoventricular premature contraction (X) arises near the middle of the tissue and a P wave is not seen In C the auriculoventricular premature contraction (P) arises low in the auriculoventricular bundle and ventricular contraction precedes auricular activity so that the P wave follows the QRS complexes

ward by retrograde conduction to the auricles and initiates their contraction and simultaneously downward to the ventricles stimulating them If the stimulus arises high up in the junctional tissue the auricles contract first followed in 0 10 seconds or less by the ventricles if it arises in the middle of this tissue *it arrives simul*taneously at the auricles and ventricles and they contract synchronously if arising at the lower part of the junctional tissue the stimulus arrives at the ventricles first causes them to contract, and arriving later at the auricles results in their contraction accordingly, in the electrocardiograms the P wave falls in front of (Fig 132A) during (Fig *132B*) or after the QRS complex (Fig 132C)

One auriculoventricular premature contraction occasionally initiates two ventricular contractions The stimulus traverses the auriculoventricular bundle and initiates the ventricular contraction and in passing backward to the auricles, stimulates their contraction this auricular impulse spreads through the auricular muscle and arriving at the auriculoventricular tissue passes down the bundle if this tissue is no longer refractory is distributed again to the ventricles and causes another ventricular systole provided the ventricles have also recovered from their refractoriness (Fig 149A and B)

TREATMENT —When treatment is required it is similar to that given for auricular premature contractions namely sedation or *digitalis*

Auriculoventricular Paroxysmal Tachycardia —This term designates a rapid regular beating of the heart controlled by stimuli arising in the junctional tissue and characterized by sudden onset and *sudden* offset It may be looked upon as a succession of auriculoventricular premature contractions The excitation wave passes upward to the auricles initiating their contraction and also downward to the ventricles stimulating them The rate is usually around 150-200 per minute but may be slower or more rapid

ETIOLOGY —It occurs in all age groups both in subjects with normal hearts and in those with organic disease It occurs in acute rheumatic fever and coronary occlusion and in patients with Wolff Parkinson White syndrome It may be transient or persist for days

PATHOLOGIC PHYSIOLOGY —*Auriculoventricular* paroxysmal tachycardia is associated with decreased cardiac output per minute and the stroke volume may fall as low as 12 cc from a normal level of 60 cc the circulation time may be prolonged and the heart dilates The blood pressure may fall and heart failure may appear

SYMPTOMS—Symptoms are similar to those associated with auricular paroxysmal tachycardia

DIAGNOSIS—Clinically this cannot be differentiated from auricular paroxysmal tachycardia although the rate may be more rapid The diagnosis is made in the electrocardiogram the P wave falls before (0 10 seconds or less) (Fig 133A and B) during (Fig 133C) or after the QRS complex (Fig 133D) Occasionally supraventricular paroxysmal tachycardia is diagnosed if the origin cannot be more accurately localized

PROGNOSIS—Attacks may occur for many years without the appearance of signs of cardiac disease Electrocardiographic changes may persist several weeks after an attack

TREATMENT—Treatment is similar to that for auricular paroxysmal tachycardia Digitalization is the most effective means

Auriculoventricular or nodal rhythm occurs when pacemaking is dislocated from the sinus node to the auriculoventricular tissue so that a focus in this tissue controls the beating of auricles as well as ventricles The rate is usually slower around 40 per minute than the discharge from the sinus node The sequence is usually regular

ETIOLOGY—The dislocation of pacemaking to this node is precipitated either by factors depressing the sinus discharges by

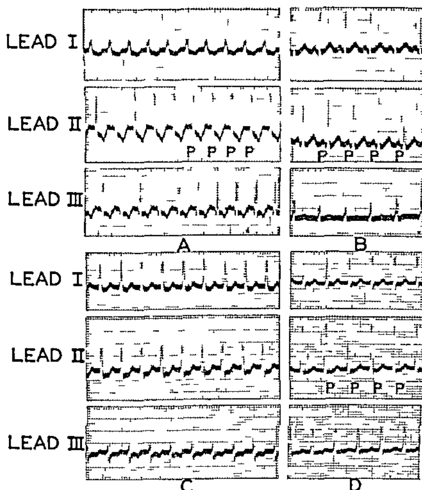


Fig 133—In A and B are shown the three standard leads illustrating auriculoventricular paroxysmal tachycardia (rate 206 and 150 per minute respectively) in which the P waves (PPP) fall in front of the QRS In C are shown the three standard leads illustrating auriculoventricular paroxysmal tachycardia (rate 176) in which the P waves are not seen and are presumably concealed in the QRS complexes and in D the P waves (PPP) follow the QRS complexes (rate 172 per minute) Increasing the speed of the electrocardiograph film or loosening the galvanometer string may aid in identifying the P waves

vagal stimulation or those increasing the irritability of the auriculoventricular tissue by sympathetic nerve stimulation The rhythm occurs more commonly in subjects having heart disease It may result from digitalis, sometimes in doses less than the full therapeutic amount and also after atropine On the other hand atropine may restore sinus pacemaking It is encountered in acute infections

Pathologic Physiology —Studies of the circulation during this rhythm have not been reported

Symptoms —The rhythm causes no symptoms unless the rate is very slow

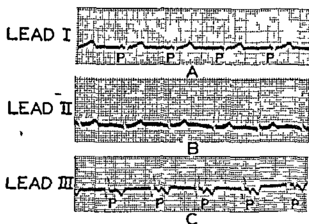


Fig 134 —In A is shown Lead I illustrating nodal rhythm (rate 66 per min) in which the P waves (PPP) precede the QRS the P R time is 0 08 to 0 09 sec In B is shown Lead II illustrating nodal rhythm (rate 79 per min) in which the P waves are not seen and it appears that the P and QRS occur simultaneously In C is shown Lead III of nodal rhythm in which the focus for pacemaking is low in the bundle so that the ventricular complexes (QRS) (65 per min) occur first followed by the auricular contractions (PPP)

Diagnosis —The diagnosis should be suspected when the rate is slow and large pulsations occur in the jugular veins resulting from simultaneous contraction of auricles and ventricles *Electrocardiograms differentiate it from complete block and sinus bradycardia* The stimuli may arise in any part of the auriculoventricular tissue so that the P waves in the electrocardiogram precede (Fig 134A) occur simultaneously with (Fig 134B) follow the QRS complex (Fig 134C) or shuttle up and down (Fig 135A)

Prognosis —Normal rhythm is restored when the precipitating factors are eliminated

Treatment —It is usually very transient but may persist for days It requires no special therapy If digitalis is implicated normal rhythm follows its elimination Heart failure, however takes precedence in therapy

Wandering Pacemaker —When pacemaking shifts back and forth from the sinus to the auriculoventricular node the rhythm is designated as *wandering pacemaker* It is commonly transient but may be persistent It very rarely follows digitalization It is frequently observed in normal individuals especially athletes with bradycardia and during deep breathing It may be evidence of carotid sinus hyperactivity In electrocardiograms the P waves shift location with respect to the QRS complex indicating that the site of impulse formation shifts from the sinus node to the upper part of the auriculoventricular node then moves gradually down the auriculoventricular tissues after which it retraces its course up the junctional tissue back to the sinus node (Fig 135B)

Conduction Defects —*Heart block* refers to auriculoventricular heart block and occurs when stimuli arising in the sinus node or auricles are delayed or obstructed in their passage down the auriculoventricular bundle Defect in the main bundle is more common than in its right and left branches

When there is delay in conducting the sinus impulse the interval from the beginning of auricular activity to the onset of ventricular activity in the electrocardiogram exceeds 0 20 seconds *This is designated prolonged P R conduction time or first degree heart block* (Fig 136A) When impulses are blocked from reaching the ventricles so that ventricular contractions fail to occur there is *second degree partial* or *incomplete heart block* which may assume several patterns In the *Wenckebach phenomenon* the delay in conduction increases progressively until an impulse is blocked and a "dropped beat" occurs the bundle transmits the next sinus impulse after which the progressive increase in P R time recurs (Fig 136B) Every third (3 2 heart block) fourth fifth sixth seventh or eighth stimulus may be blocked At other times every second or every second and third impulses are blocked giving rise to 2 1 (Fig 136C) and 3 1 (Fig *136D*) block in which there are two and three auricular contractions to one ventricular beat respec

tively These are *high grade heart block* Finally when obstruction to the passage of sinus impulses is total *complete heart block* or *complete auriculoventricular dissociation* is present (Figs 136E F, 137A) When this occurs the ventricles escape and contract at their own inherent rhythm which is usually slow thirty to forty per minute and rarely rapid *idioventricular rhythm* prevails (Figs 136E F 137A) The auricles may beat regularly (Figs 136F 137A) or fibrillate (Fig 136E)

Etiology—Alterations in the conducting system resulting in heart block may be occasioned by (1) structural damage (2) toxic effect of drugs (3) nutritional changes and (4) vagal effects Conduction changes are accepted as criteria of rheumatic activity which may cause all degrees of transient or permanent block Any degree of block occurs in arteriosclerosis and in coronary occlusion it may be transient or chronic Likewise diphtheria may cause any degree of block chronic or transient especially complete block Congenital heart block especially when complete may be associated with interventricular septal defect Digitalis results in any grade of block which is not necessary for a therapeutic effect Acetyl beta methylcholine chloride induces conduction defects through its stimulation of parasympathetic nerve effects Nutritional or functional changes probably cause the alterations in uremia and in myxedema Carotid sinus pressure may induce any grade block and cardiac standstill (Fig 137B and C)

Morbid Anatomy—In functional or nutritional block pathologic lesions are not expected In organic block anatomic lesions

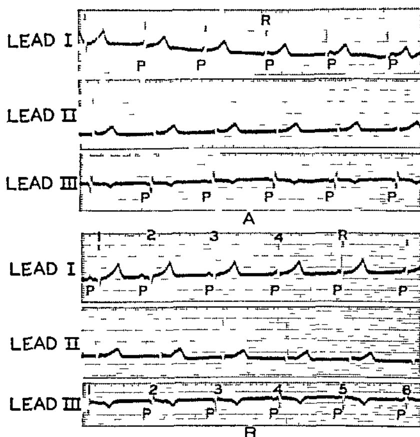


Fig 135—In A is shown three leads of nodal rhythm (rate 50 per min) in which the focus for pacemaking shuttles up and down the junctional tissue indicated by the changing position of the P waves (PPP) to the QRS complexes In B is shown three leads of *wandering pacemaker* Complexes 1 and 2 arise in the sinus node (58 per minute) 3 shifts to high up in the junctional tissue (rate 48 per min) the place of origin of the excitation wave then gradually moves down the bundle (shifting position of P waves) in Leads I and II and in Lead III the site is again high up (complexes 2 and 3) then in 4-5-6 activity is restored to the sinus node

are detected very frequently, but may not be greater than in another heart in which defects are not recorded The lack of correlation between the presence of block and the microscopic picture is not surprising since the integrity of a few fibers may be sufficient to transmit the excitation wave Inflammatory changes in rheumatic fever may involve

First degree heart block causes no symptoms and probably no marked alterations in cardiac function The P R interval in the electrocardiogram exceeds 0 20 seconds (Fig 136A)

Second Degree Heart Block—PATHOLOGIC PHYSIOLOGY—Occasional block is probably associated with no marked change in cardiac

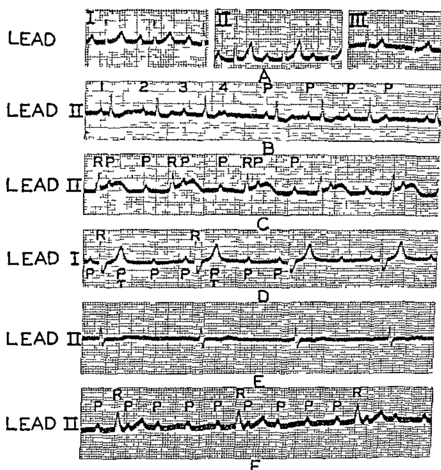


Fig 136—In A is shown three standard leads with P R conduction prolonged to 0.32 sec in Lead II In B is shown in Lead II gradual prolongation of P R from 0 20 in 1st to 0 27 in 2d to 0 39 in the 3rd complex and the fourth P wave is blocked this pattern is then repeated (Wenckebach phenomenon) In C is shown Lead II of 2 1 heart block (P=P waves R= ventricular waves) with prolonged P R time to 0 41 seconds (ventricular rate 48 auricular rate 96) *The blocked P wave appears on the hump of the T waves* In D is shown Lead I of 3 1 heart block (PPP=P waves and R=ventricular complexes) (ventricular rate 37 auricular rate 111) In E is shown auricular fibrillation with complete heart block and idioventricular rhythm the ventricular rate 37 in Lead II In F is shown Lead II of complete heart block with the auricles (PPP) continuing to contract at the rate of the sinus node discharge (ventricular rate 30 auricular rate 120) *Idioventricular rhythm with bundle* branch block is present (QRS prolonged to 0 12 seconds)

the conduction system although the changes are also attributed to vagal effects Arteriosclerosis causes block either by myocardial fibrosis involving the bundle or by decrease in blood supply by narrowing or closure of coronary vessels supplying this tissue There may be diffuse syphilitic involvement or gumma formation

function *2 1 block results in decrease in* cardiac output per minute with prolongation of the circulation time

SYMPTOMS—Patients are usually unaware of occasional block when occurring frequently they may complain of the pause of the forceful beat after the pause or palpitation In 2 1 block they may complain of

the slow forceful beating dyspnea and rarely exhibit other signs of failure

DIAGNOSIS —During digitalis therapy or rheumatic fever the diagnosis is frequently possible When there is occasional block a sequence of regular beats followed by a pause will be detected on auscultation then the regular sequence recurs The pause is also apparent in the pulse The irregularity differs from a premature contraction in not being preceded by an early beat The pause may equal two regular cycles When high grade block is present the ventricular rate may be slow around forty per minute when the ventricular rate suddenly halves 2 1 heart block should be considered (Fig 136C) Auricular contractions may be heard in the middle of the long pauses and one or two a waves may be seen in the jugular pulse The electrocardiogram shows the relationship between P and QRS complexes (Fig 136B C and D)

PROGNOSIS OF FIRST AND SECOND DEGREE HEART BLOCK —In rheumatic fever block usually disappears with recovery when resulting from digitalis normal conduction is restored with its elimination In luetic and arteriosclerotic heart diseases or after coronary occlusion block indicates myocardial damage and makes the prognosis more serious

TREATMENT —Incomplete block usually requires no treatment Digitalis when implicated is omitted for a few days or the dose diminished If the patient complains of irregularity atropine 0 0006 Gm 1/100 gr) may abolish it Digitalis can usually be given when necessary even though high grade block is present without increasing the block

Complete Heart Block —ETIOLOGY —Complete block is most common in arteriosclerotic heart disease with or without coronary occlusion less common in congenital heart disease following diphtheria or digitalis intoxication

PATHOLOGIC PHYSIOLOGY — Complete block is usually associated with marked decrease in the cardiac output *per minute* but the stroke volume is usually increased and may be as much as 90 cc per beat The circulation time may be prolonged In complete block the heart rate cannot increase appreciably to provide increase in cardiac output As a compensatory mechanism the organism decreases its basal metabolic rate The systolic blood pressure may be elevated

SYMPTOMS —When complete block has become established patients may be without symptoms when at rest but experience dyspnea and dizziness on exertion They may be unaware of the rhythm or may complain of the slow forceful beating of the heart Other patients suffer the Stokes Adams syndrome characterized by syncope with convulsions or milder symptoms of dizziness and faintness because there may be several seconds of ventricular asystole at the onset of complete block before the idioventricular center becomes active During this time the circulation is at a standstill In recurrent complete block the Stokes Adams syndrome may recur with each onset When complete block has become established and adjustments have been made the cardiac output is usually sufficient to supply the body needs and the patient recovers from syncope and convulsions and may remain without symptoms On further slowing of the rate however to 15 or 20 per minute syncope will recur Asystole and syncope may be transient or persist for several seconds Occasionally patients complain of headache weakness and fatigue Heart failure may result

DIAGNOSIS —Complete heart block is to be suspected when the heart beats regularly around thirty five per minute and the patient complains of syncopal attacks It is to be differentiated from 2 1 heart block and sinus bradycardia Exercise does not increase the rate appreciably The cardiac and radial rates correspond Auricular beats may be heard at a more rapid rate than the ventricular ones a waves may be identified during the ventricular intervals and a ratio is not apparent The first heart sound changes due to the shifting relationship of auricular to ventricular systole (Fig 137A) Fluoroscopy reveals independent auricular and ventricular contractions Electrocardiograms confirm the diagnosis (Figs 136E F 137A) When digitalis is being given in auricular fibrillation the onset of a slow *regular* ventricular sequence suggests complete block (Fig 136E)

PROGNOSIS —Complete block usually disappears with recovery from rheumatic car

ditis and diphtheria Persistence after diphtheria is compatible with longevity In luetic and arteriosclerotic heart disease and after coronary occlusion it indicates progressive damage to heart muscle and makes the prognosis more serious Bundle branch block increases the hazards Compensated patients tolerate surgical operations Death follows prolonged ventricular asystole or too great ventricular slowing Complete block occasionally disappears after being present for many months

TREATMENT —When complete block has become established treatment is usually not required Patients lead active lives with not only because it is not known whether the patient will suffer another seizure shortly after recovery, but also on the chance that the idioventricular center will take over promptly If the attack is prolonged intracardiac injection of adrenalin is indicated In chronic complete block, patients may require adrenalin every two to three hours for many days due to sudden decline in rate below that established For more prolonged effect ephedrine sulfate 20 to 30 mg (⅓ to ½ gr) three times a day orally may be beneficial In other instances barium chloride 30 to 40 mg (½ to ⅔ gr) three or four times a day orally increases ventricular irritability

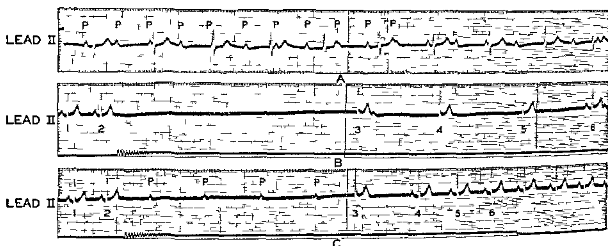


Fig 137 —In A is shown a long strip of Lead II showing complete heart block with idioventricular rhythm, auricular rate 75 and the ventricular rate 43 per minute At times 3 1 or 4 1 heart block may be diagnosed unless a long enough strip is taken for the P waves and QRS complexes to get out of step The R R interval in which the QRS falls may be short B shows in lead II asystole for 6 sec resulting from right carotid sinus pressure ventricular escape finally occurring at 3 with three complexes of idioventricular rhythm and reversion to normal sinus rhythm at 6 while pressure is still maintained The signal at the bottom indicates the application of pressure C shows in Lead II complete heart block with ventricular asystole for 6 sec on the application of pressure to the left carotid sinus The auricular rate (PPP) is 43 per minute There is ventricular escape at 3 followed by return to normal sinus rhythm at 4 while pressure is still maintained The signal indicates onset and release of pressure

restriction of overexertion If heart failure occurs digitalis is used It is unusual for its vagal effects to retard the ventricles further When due to digitalis normal conduction follows its elimination

When Stokes Adams attacks occur frequently 0 5 cc to 1 0 cc (7½ to 15 minims) adrenalin 1 1000 is given hypodermically Its effect lasts one to two hours It increases the irritability of the ventricular pacemaker and of ventricular muscle and may prevent long periods of asystole as well as increase the rate Although it may be useless to give adrenalin during Stokes Adams syncope it is advisable to give it at once nevertheless

Thyroid extract 0 1 Gm (1½ gr) once to three times a day may be tried It is used cautiously not only because it is inadvisable to increase the basal metabolic rate in patients with coronary artery disease but also because fall in basal metabolic rate is one of the compensatory mechanisms in complete block Atropine 0 5 to 1 0 mg (½₀ to ⅟₆₀ gr orally or hypodermically several times daily may decrease vagal block

Bundle branch block or intraventricular block occurs when the excitation wave is impeded in its passage down the right or left branch of the auriculoventricular bundle an abnormality recorded in electrocardio

grams (Figs 138A C and D) Excitation of the ventricle supplied by that branch is delayed and asynchronism of ventricular contraction results The rhythm is unaffected

ETIOLOGY—It occurs most commonly in arteriosclerotic and hypertensive heart diseases and is most common in older individuals It follows myocardial infarction Left bundle branch block is more common than right probably because sclerotic changes are more common in the descending branch of the left coronary artery It occurs occasionally in rheumatic carditis and bolic phenomena (Fiedler's or isolated myocarditis)

MORBID ANATOMY—Myocardial fibrosis involving the bundles has been found when bundle branch block was recorded electrocardiographically It is however frequently impossible to differentiate microscopically the blocked from the unblocked side or from the bundles in hearts not exhibiting this defect In them block may be due to decreased blood supply to the affected bundle Structural changes are not expected if the defect was transient.

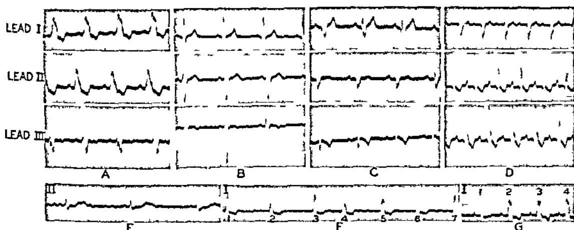


Fig 138—A illustrates three leads of left bundle branch block, concordant type in which the major QRS is upward in Lead I and T waves opposite in direction to the major deflection The QRS interval is 0 17 to 0 18 sec in Lead II B illustrates three leads of left bundle branch block discordant type in which T waves are in the same direction as the major QRS deflection and the QRS interval is 0 14 sec C illustrates three leads of bundle branch block of the wide S wave type (QRS time 0 13 sec) and in D three leads of right bundle branch block of the wide S wave type (QRS time 0 13 sec) and in D three leads of right bundle branch block concordant type T waves in opposite direction to the major QRS deflection (QRS time 0 12 sec) The discordant type in which the T waves are in the same direction as the major QRS deflection is not recorded In E is shown Lead II illustrating bundle branch block (QRS time 0 12 sec) with complete heart block in auricular fibrillation (ventricular rate 34 per minute) (see Fig 136F for bundle branch block with complete heart block in which the sinus node is operative) In F is shown Lead I of auricular fibrillation in which in complexes 1-2-3 the QRS time is 0 09 to 0 10 seconds (normal) followed in 4-5-6 by bundle branch block (QRS 0 11 to 0 12 seconds) and then by normal conduction in 7 In G is shown Lead I normal sinus rhythm with transition from normal QRS (0 08 sec) in 1 to bundle branch block (QRS 0 12 to 0 13 sec.) in complexes 2-3-4

in chronic valvular disease (aortic stenosis and insufficiency) Gumma and diffuse syphilitic involvement as well as diphtheria are less commonly implicated Bundle branch block is occasionally functional in uremia and a fatigue manifestation during tachycardia It may be a toxic effect of quinidine and rarely has been attributed to digitalis It occurs in association with a short P R conduction (Wolfe Parkinson White syndrome) (Fig 139) It is seen in acute myocarditis of obscure origin associated with cardiac enlargement heart failure and em

PATHOLOGIC PHYSIOLOGY—The effect of onset of bundle branch block on cardiac function is not known The lesion occurs most frequently in hearts subject to myocardial damage in which the functional capacity may be already reduced

SYMPTOMS—There are no symptoms attributable to bundle branch block

DIAGNOSIS.—The clinical diagnosis cannot be made with certainty Gallop rhythm a bifid apex thrust and reduplication of one or both heart sounds suggest its presence A bifid apex beat may be exaggerated by a

strip of paper applied as a lever at the point of maximal impulse Pulsus alternans may be present The QRS time exceeds 0 10 seconds usually 0 12 seconds or longer (Fig 138) Occasionally every other beat shows block There may be normal P-R conduction or any degree of auriculoventricular block (Figs 138D and 136F)

Prognosis—Bundle branch block carries a grave prognosis It is more commonly permanent than transient (Fig 138F and G) Prognostic significance appears to derive from electrocardiographic patterns The annual death rate for all types is highest in the first year after discovery being greatest for the *concordant* types (Fig 138A and D) less for the *discordant* types (Fig 138B)

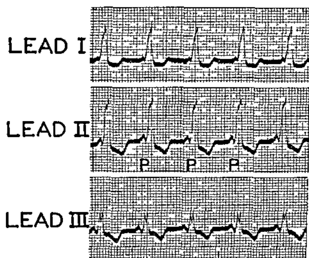


Fig 139—In this figure is shown an example of the short P R (0 07 to 0 08 sec) and the long QRS (0 12 sec) or Wolff Parkinson White syndrome

still less for the *wide S wave* types (Fig 138C) From then on the earliest and greatest mortality is found in those with the concordant types the longest survival and lowest death rate are found in those exhibiting the wide S wave types and intermediate length of survival in those showing the discordant types After the first year the life expectancy curve in the wide S wave type roughly parallels that of the normal population Ten years after discovery more than one third of the wide S wave type patients are still alive but only one sixth of the concordant types and one quarter of the discordant types These statements do not apply to the short P R long QRS syndrome (Fig 139)

Treatment—In most instances specific treatment is not indicated It may disappear in uremia when hypertonic glucose is given intravenously It may disappear with recovery from heart failure

Wolff Parkinson White syndrome is a conduction defect in the electrocardiogram characterized by a *short P R interval and prolonged QRS time* (Fig 139) It is usually an accidental finding in individuals without evidence of organic heart disease A few patients have other congenital defects such as interventricular septal communication Patients are prone to attacks of paroxysmal rhythms most commonly auricular or nodal and less frequently ventricular tachycardia and rarely to auricular flutter and fibrillation One explanation of this syndrome is the presence of a congenital accessory pathway of conduction such as the bundle of Kent bridging the auricles and ventricles The short P R time would be accounted for if this accessory pathway offered a shorter and more rapid route for conduction from auricles to ventricles the long QRS would be explained by asynchronous contraction of the two ventricles one ventricular contraction being initiated by the stimulus which has bridged the gap by the bundle of Kent and the other one contracting a later time by the excitation wave traversing the usual pathway down its bundle Restoration of normal P R and QRS intervals may take place with atropine and exercise suggesting that vagal affects underlie this phenomenon Both digitalis and quinidine have restored normal relationships in others

Prognosis—This defect does not appear to carry a serious prognosis except that it predisposes to paroxysmal rhythms and may be associated with other congenital cardiac defects

Ventricular Rhythms—*Idioventricular Rhythm*—With the onset of complete heart block or auricular standstill the ventricles beat in response to stimuli from the idioventricular center which is located in the auriculoventricular bundle just before its bifurcation It discharges impulses usually at a slow rate around thirty five per minute The QRS complex in the electrocardiogram has a supraventricular form (Figs 136E 137A) unless there is a bundle branch de

fect (Fig 136F and 139F) Rarely when the site of origin is in the ventricular muscle below the bifurcation the complexes resemble ventricular premature contractions Due to the block the impulses do not pass backward to the auricles Idioventricular rhythm differs from auriculoventricular rhythm in which stimuli arising in the auriculoventricular tissue control both auricular and ventricular activity

Ventricular Escape—Occasionally when the sinus discharges are greatly retarded and the auriculoventricular node is also depressed there may be ventricular escape and one or more beats arise from the idioventricular center It occurs in normal individuals and after carotid sinus stimulation The QRS complex is usually of the supraventricular form without a preceding P wave (Figs 125B 137B and C) because of retrograde block it may however be of aberrant form

Ventricular Premature Contractions—If an abnormal stimulus arises in the right or left ventricle a ventricular premature contraction results The impulse spreads over the ventricles and up to the auriculoventricular bundle and node but *usually* not back to the auricles so that the dominant rhythm is uninterrupted occasionally however retrograde conduction to the auricles occurs The normal impulse from the sinus node passing down the auriculoventricular system usually finds the ventricles refractory having just contracted prematurely

ETIOLOGY—Stimuli causing ventricular premature contractions have been elicited in man *mechanically* (1) by tapping over the ventricle which lies directly under the skin and muscle in a defect of the thoracic cage caused by previous removal of ribs and (2) during pericardiectomy They have been induced *electrically* during drainage of the pericardial cavity They occur more commonly in the older individuals Forced respiration breath holding or excitement may incite them They are common in organic heart disease but more frequently no other cardiac signs are detected They occur in acute infections especially acute rheumatic fever acute tonsillitis and pneumonia in arteriosclerotic hypertensive and chronic rheumatic valvular heart diseases and following coronary thrombosis They may result from nervous tension loss of sleep coffee and cigarettes and from overdigitalization when coupled rhythm may appear (p 1142) On the other hand they may be a manifestation of heart failure and may disappear with digitalization They may precede ventricular paroxysmal tachycardia

PATHOLOGIC PHYSIOLOGY—Occasional ventricular premature contractions do not alter the functional capacity of the heart but when they occur frequently and persistently the cardiac output is probably decreased

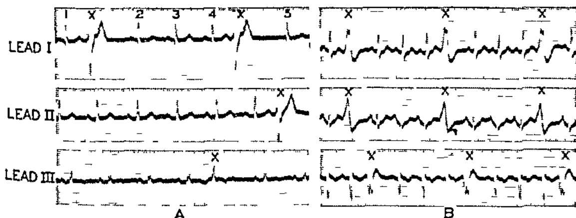


Fig 140—In A are shown three leads illustrating left ventricular premature contractions (X) There is compensatory pause In Lead I the interval 1 to 2 equals twice the regular intervals 2–3 or equals 2 to 4 In B are shown three leads illustrating right ventricular premature contractions (X) after every third normal contraction The pause after the ventricular premature contractions is compensatory If the main QRS deflection is upward in Lead I the premature contraction arises in the right ventricle (B) and if downward, in the left ventricle (A) The form of QRS in Leads II and III is dependent upon the origin of the premature contractions in the apical middle or basal part of the heart

strip of paper applied as a lever at the point of maximal impulse Pulsus alternans may be present The QRS time exceeds 0 10 seconds usually 0 12 seconds or longer (Fig 138) Occasionally every other beat shows block There may be normal P R conduction or any degree of auriculoventricular block (Figs 138D and 136F)

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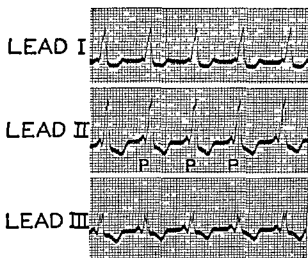


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10 Gm (15 gr) twice or three times a day is very frequently effective and is the drug of choice. If the premature contractions result from digitalis the drug is stopped for a few days or the ration decreased Except is used over long periods toxic effects must be avoided Potassium phosphate or chloride or papaverine may abolish them (p 1117)

Interpolated Premature Contractions — Premature contractions are interpolated

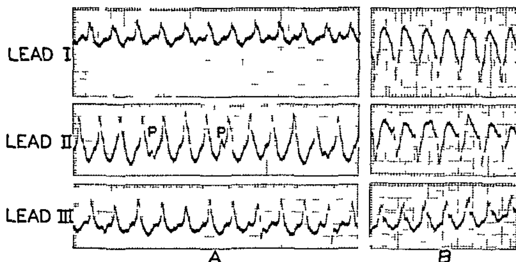


Fig 142 — In A are shown the three leads of ventricular paroxysmal tachycardia from the right ventricle (rate 182 per minute) and B from the left ventricle (rate 200 per minute) The auricles are contracting at their usual slower rate indicated by P in Lead II of A In B the standardization of the string is for 2 cm instead of 1 cm to magnify the waves

when they are a manifestation of congestive failure digitalis is not used because it may increase their number If they are very numerous or multiple digitalis may precipitate ventricular paroxysmal tachycardia or ventricular fibrillation If other measures fail when they occur between two normal heart beats without disturbing the rhythm they are true *extrasystoles* In the electrocardiogram if the premature stimulus occurs near the middle of the R R interval and the ventricles are no longer refractory a premature contraction will occur and recovery will again take place so that when the next normal auricular impulse arrives the conduction tissue is receptive to transmit it

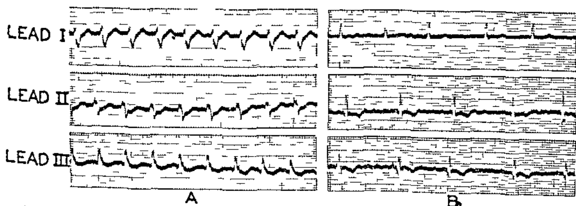


Fig 143 — In A are shown the three standard leads of ventricular paroxysmal tachycardia (rate 125 per minute) from the left ventricle during the paroxysm and in B after reversion to auricular fibrillation (ventricle rate approximately 75 per minute)

quinidine sulfate 0 2 Gm (3 gr) twice or three times a day may abolish them If successful the drug *may frequently* be discontinued without their recurrence If the drug

SYMPTOMS—The symptoms do not differ significantly from those experienced with auricular premature contractions Ventricular ones more commonly give a sense of fulness in the neck due to the auricles and ventricles contracting synchronously When persistent they may be associated with dizziness Dry cough may occur

DIAGNOSIS—Ventricular premature contractions can usually be diagnosed clinically On auscultation the beat is premature the radial pulse may be premature or may show a pulse deficit if the beat occurred so early while the ventricles are in systole Ventricular premature contractions may disappear on exercise The diagnosis is made in the electrocardiogram when the QRS complex which is not preceded by or related to a P wave is wide and split, and the T wave usually opposite in direction to the main QRS deflection Ventricular premature contractions may occur irregularly or after a recurrent pattern Occasionally retrograde conduction occurs and the excitation wave initiates an auricular premature contraction the stimulus of this auricular premature con-

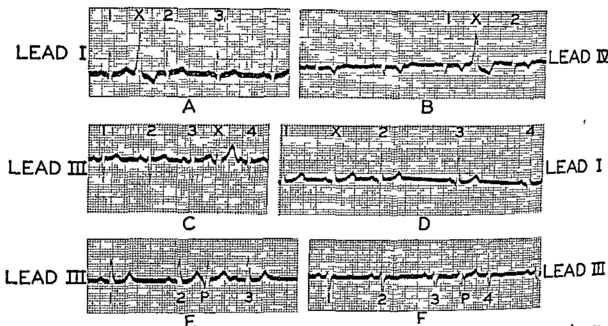


FIG 141—In A and B are Lead I and Lead IV respectively illustrating interpolated right ventricular premature contractions between normal complexes 1 and 2 (X) (see text) In C is shown in Lead I an interpolated auricular premature contraction (X) between normal complexes 3 and 4 and in D in Lead III interpolated auricular premature contraction (X) between normal complexes 1 and 2 QRS complexes of the premature beats are supraventricular in form In E is reproduced Lead III showing an interpolated auriculoventricular premature contraction in which the P wave (P) precedes the QRS between normal beats 2 and 3 and in F Lead III, the P wave (P) of the auriculoventricular premature contraction falls after the QRS between normal beats 3 and 4

that insufficient blood was available to form a radial pulse There is an appreciable pause after the premature beat until the next regular one occurs This *compensatory pause* may be too short however to make differentiation from supraventricular premature contraction certain The interval from the last usual beat to the first one after the premature beat equals two normal cycles (Figs 140A and B) Ventricular premature contractions have a clicking quality There may be a large wave in the jugular vein coinciding with the ventricular premature contractions due to the auricles contracting traction then passes downward through the auriculoventricular tissue and excites the ventricles to contract again this one will be supraventricular in form (short QRS) (Fig 149C)

PROGNOSIS depends upon the circumstances under which the premature contractions occur and upon other evidences of heart disease

TREATMENT—When treatment is required the general principles are the same as for auricular premature contractions elimination of possible factors and use of triple bromide or luminal Triple bromide

with marked decrease in the cardiac output per minute and the stroke volume falls as low as 18 cc There is prolongation of the arm to tongue circulation time without increase in venous pressure unless heart failure supervenes The heart dilates and the blood pressure falls

Symptoms — The patient experiences symptoms similar to those of auricular paroxysmal tachycardia Occurring more commonly as a complication of heart disease however patients appear more ill

Diagnosis — Ventricular paroxysmal tachycardia is to be differentiated especially from auricular and nodal paroxysmal tachycardia The rate is commonly 150–180 slightly slower than the supraventricular forms The rhythm is slightly irregular as compared with auricular tachycardia The heart sounds may change due to the shifting relationship of the ventricular and auricular contractions Frequently a waves can be identified in the jugular vessels and are especially large when the auricles and ventricles contract simultaneously Carotid sinus pressure is ineffectual in most cases Electrocardiograms usually make certain the diagnosis The complexes have the form of ventricular premature contractions and may arise from either ventricle (Fig 142A and B) or may be alternating (Fig 144A) or the QRS complexes may vary If the preceding rhythm was normal the auricles continue to beat slowly and independent P waves appear (Fig 143A and B) The ventricular excitation waves are usually blocked from passing backward Occasionally however *retrograde* conduction to the auricles causes them to contract the sinus node being superseded If auricular paroxysmal tachycardia and bundle branch block occur together the complexes will be similar to ventricular premature contractions The detection of P waves may establish the rhythm as auricular or the occurrence of ventricular premature contractions in other records of the patient may aid in differentiation

Prognosis — Ventricular paroxysmal tachycardia is an alarming hazard when it occurs in the course of myocardial infarction Impairment in the coronary circulation associated with marked decrease in cardiac output and fall in blood pressure is shown in the T wave changes which may persist for days after reversion to normal rhythm Heart failure may be precipitated

Treatment — The patient should be in bed If the paroxysm is brief treatment is not required More commonly it persists unless measures are taken to control it most circumstances under which it occurs require its prompt abolition Quinidine is usually effective 0.2 Gm (3 gr) is given two hours later if there have been no evidences of idiosyncrasy (see auricular fibrillation) and normal rhythm has not been restored 0 4 Gm (6 gr) is given and repeated every four hours 3 0 to 4 0 Gm (45 to 60 gr) may be required in twenty four hours before reversion occurs If it is not urgent 2 0 Gm (30 gr) may be given the first day 3 0 Gm (45 gr) the next but if coronary occlusion is present restoration should be achieved promptly with the larger amounts When possible electrocardiograms should be taken Massive doses of quinidine may occasion ventricular fibrillation After restoration of normal rhythm 0 2 Gm (3 gr) twice or three times a day are given for a few days With therapy the ventricular rate declines followed by reversion to normal rhythm or auricular fibrillation It is only rarely necessary to give quinidine hydrochloride in 0 2 to 0 3 Gm (3 to 5 gr) amounts *intravenously* It does not appear warranted to give quinidine routinely after coronary occlusion to prevent this rhythm For recurrent attacks quinidine sulfate 0 2 Gm (3 gr) twice or three times a day is usually effective and patients should be instructed about its use Digitalis is usually contraindicated because it increases ventricular irritability and may precipitate ventricular fibrillation If the rhythm is not susceptible to quinidine and heart failure ensues it may however be required

Ventricular Fibrillation — In this rhythm the coordinated contraction of the ventricles is replaced by rapid irregular twitches of the ventricular muscle Its persistence is incompatible with life because the twitchings are ineffectual in expelling blood The mechanism may be a circus motion in the ventricles Brief paroxysms are not fatal Ventricular fibrillation is a cause of sudden death especially in patients with coronary artery disease It has been observed in the electrocardiograms of dying patients and of

and the ventricles are capable of responding again. Auscultation reveals three rapid beats, the middle one being the *extrasystole*. Interpolated premature contractions may arise from the auricles (Fig 141C and D), auriculoventricular tissue (Fig 141E and F), or from the ventricles (Fig 141A).

Ventricular paroxysmal tachycardia is a fairly regular rhythm with a rapid rate caused by stimuli originating from an ir

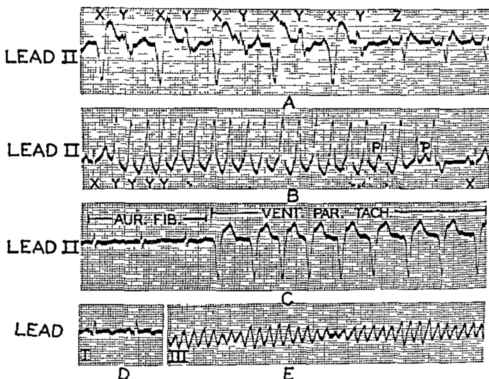


Fig 144—In A is shown in Lead II a run of ventricular paroxysmal tachycardia (134 per minute) with alternation of origin of the beats XXX and YYY followed by reversion to normal sinus rhythm at Z. In B is shown in Lead II one normal complex (X) *followed by a run of ventricular paroxysmal tachycardia* YYY (rate 250 per minute the sequences are slightly irregular) with reversion to normal sinus rhythm at the end of the strip (X). The P waves of auricular contraction can be seen at intervals. In C in Lead II are three ventricular complexes during auricular fibrillation (ventricular rate 80 per minute) with onset of ventricular paroxysmal *tachycardia in which the ventricular sequences are irregular (rate approximately 120 per minute)*. In D is shown Lead I of electrocardiogram of a patient showing normal rhythm which had changed to ventricular fibrillation (E) a few minutes later when Lead III was being taken. The ventricular complexes are somewhat irregular and of bizarre and changing form.

ritable focus in one of the ventricles characterized by sudden onset and sudden offset. It may be considered a succession of premature contractions. If the preceding rhythm was normal the sinus impulses continue and the auricles contract at their usual rate (Fig 142A and B). Auricular fibrillation may however be present (Fig 143A and B). Ventricular paroxysmal tachycardia may result from a circus motion in the ventricles. The ventricular rate is commonly 150–200, *rarely greater than* 220. It may persist for a few beats (Fig 144B and C), several minutes, hours or many days and be resistant to treatment.

Etiology.—Ventricular paroxysmal tachycardia occurs more commonly in organic heart disease than the auricular type but it is found occasionally in normal subjects. Ventricular premature contractions may precede its onset. It is most common in the later decades when arteriosclerotic and hypertensive heart diseases occur. It may follow coronary occlusion and at other times has been thought to lead to myocardial infarction due to the fall in blood pressure or decrease in coronary circulation. It occurs in acute rheumatic fever, in subjects with Wolff Parkinson White syndrome and transiently during pericardiectomy. It may be a manifestation of digitalis toxicity.

Pathologic Physiology.—It is associated

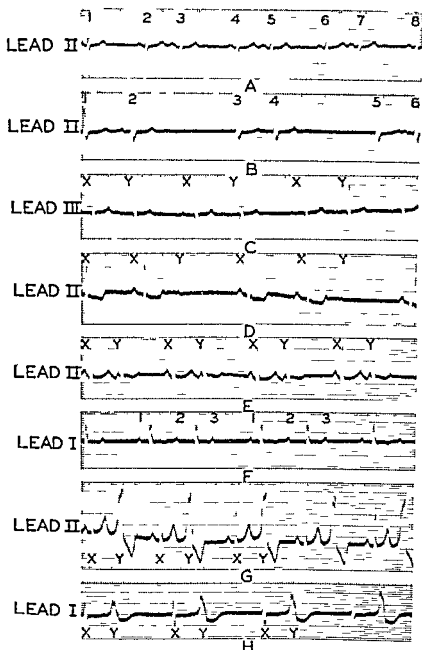


Fig 146—In A is shown in Lead II coupled rhythm due to recurrent sino-auricular block Intervals 1 to 2 3 to 4 5 to 6 and 7 to 8 show sino-auricular block The regular sequence is 2 to 3 4 to 5 and 6 to 7 which was present in Lead I with only an occasional sino-auricular block In B is shown in Lead II coupled rhythm due to normal sinus rhythm with recurrent sino-auricular block and ventricular escape Complexes 2 4 6 are normal rhythm and 1 3 5 are ventricular escape Intervals 2 to 3 4 to 5 are sino-auricular block In C is shown Lead III of coupled rhythm due to recurrent auricular premature contractions X=normal rhythm complex Y=auricular premature contractions In D is shown in Lead II coupled rhythm due to recurrent auricular premature contractions which are blocked X=normal beat Y=auricular premature contractions blocked the form of these P waves is different from the normal P waves In E is shown Lead II of coupled rhythm due to recurrent auriculoventricular premature contractions the P waves in front of the QRS X=normal beats Y=auriculoventricular premature contractions In F is shown in Lead I coupled rhythm due to incomplete heart block in which every third (3) P wave is blocked P waves are indicated as 1 2 3 In G is shown Lead II of basic normal rhythm with coupling due to recurrent ventricular premature contractions X=normal beats Y=ventricular premature contraction In H is shown Lead I of auricular fibrillation with coupled rhythm due to recurrent ventricular premature contractions X=normal beats Y=ventricular premature contractions

subjects during electrocution It may follow ventricular paroxysmal tachycardia and massive doses of quinidine and digitalis Paroxysms which have been diagnosed were accompanied by Stokes Adams like attacks and were characterized by the absence of pulse and of heart sounds Quinidine may prevent attacks even though massive doses may induce them In the electrocardiogram wide *QRS* complexes occur irregularly with bizarre and changing form (Fig 144D and E)

Pulsus Alternans—When the volume of the radial pulse alternates between a large and a small one and the sequence is regular *pulsus alternans* is present It may result because all of the muscle fibers of the heart do not contract with equal force at each systole This may be due to prolongation of the refractory period of some fibers Those beats in which only part of the muscle fibers take part are associated with a small stroke volume and a small pulse Pulsus alternans is found occasionally in luetic heart disease but most commonly in the older age groups in which the arteriosclerotic and hypertensive forms and coronary occlusion predominate It occurs in early and marked heart failure There are no symptoms attributable to pulsus alternans

Diagnosis is made by detection of alternation in volume of the radial pulse on palpitation which is easily observed while taking the blood pressure *Alternation* may also appear in the electrocardiogram tall QRS complexes coinciding with the larger radial pulse and lower ones with the smaller radial pulse (*Fig 145A and B*), *or the* reverse Pulsus alternans should not be confused with coupled rhythm

Treatment is directed to the underlying condition It may disappear when digitalis is given It carries a grave *prognosis* patients surviving only a few years after its discovery It may be transient but if it persists or recurs death may occur in a few months Both pulsus alternans and *electrical alternans* may occur transiently in paroxysmal tachycardia or auricular flutter in which there is not the same grave prognosis

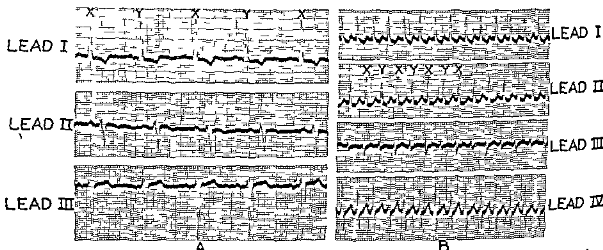


Fig 145—In A are reproduced three leads of an electrocardiogram showing normal rhythm illustrating electrical alternans The QRS complexes marked X are taller than the alternate ones marked Y In B are shown four leads of an electrocardiogram illustrating electrical alternans occurring in auriculoventricular paroxysmal tachycardia (rate 214 per minute) The tall QRS complexes (X) alternate with the lower ones (Y)

Coupled Rhythm—Coupled rhythm refers to recurrent grouping of the heart beats in pairs followed by a pause The radial pulse may also show coupling Coupled rhythm at the apex is most commonly caused by (1) ventricular premature contractions with the long compensatory pause regularly following each normal systole (Fig 146C and H) The radial pulse may be coupled also if the ventricular contractions occur late enough for sufficient ventricular filling if the radial pulse is lacking its rate is half the apical The diagnosis of coupled rhythm due to ventricular premature contractions can usually be made clinically especially if the patient is taking digitalis and auricular fibrillation is present (Fig 146H) Coupled rhythm at the apex and in the radial pulse may also be due to regularly recurring (2) auricular premature con

ing between 2 1 and 3 1 or 4 1 It may also be due to (7) incomplete heart block when every third auricular stimulus is blocked (Fig 146F) One notion of regularly recurring premature contractions is that of the *parasystole* an ectopic pacemaker is constantly and regularly initiating stimuli in much the same fashion as the sinus or auriculoventricular node when the refractory state of the muscle is appropriate and does not interfere the impulse from this new focus gives rise to premature contractions which may be after every normal beat or according to any other fixed pattern (Figs 146C E G 147A B C)

Common causes of *trigeminal* rhythm are (1) premature contractions after every second normal beat the long pause after the premature contraction making the two normal beats and the premature contraction fall together in a group of three (Fig 147A and C) (2) interpolated premature contractions (Fig 141) and (3) regularly recurring incomplete heart block every fourth auricular contraction being blocked

Ventricular Preponderance —From electrocardiograms inference may be drawn about ventricular muscle mass In the most common normal electrocardiogram the major QRS deflections are upright in all three leads and the amplitude of QRS_2 is greater than QRS_1 or QRS_3 (Fig 148A) When the major QRS deflection is upward in Lead I and downward in Lead III *left axis deviation or left ventricular preponderance* is present (Fig 148B), when the major QRS deflection is downward in I and upward in III *right axis deviation* or *right ventricular preponderance* is present (Fig 148C) There are gradations between these three types A calculated electrical axis between +90 and 0 is the normal zone which is designated as the normal axis deviation when the electrical axis is greater than +90 right axis deviation is present and if it is negative left axis deviation is present The position of the heart in the chest alters the axis deviation. Transverse position of the heart as seen in pyknic body types high diaphragm obesity pregnancy ascites increased intra abdominal pressure favor left axis deviation dropped heart as seen in the linear body types favors a tendency to right axis deviation as does displacement of the heart by fluid or air in the chest Left axis deviation may be associated with predominant hypertrophy of the left ventricle such as occurs in hypertension aortic stenosis aortic insufficiency and mitral insufficiency Right axis deviation is associated with preponderant enlargement of the right ventricle It is usual in the first few weeks of life It is associated with mitral stenosis pulmonic valve stenosis (congenital) and pulmonary lesions which place a strain on the right heart namely pulmonary fibrosis sclerosis of the pulmonary arteries diffuse pulmonary thrombosis emphysema and asthma

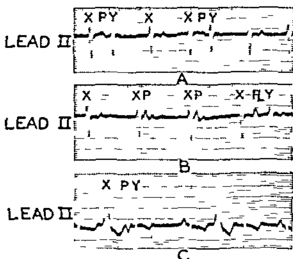


Fig 149—In A is shown auriculoventricular rhythm P waves probably in QRS (X) The excitation wave passes to the auricle by retrograde conduction and initiates an auricular excitation wave (P) which is in turn followed by ventricular contraction (Y) All the complexes have a supraventricular form This pattern is repeated In B is shown another example of nodal rhythm with P waves (P) falling after the QRS At PL the excitation initiates by retrograde conduction an auricular excitation wave (premature contraction) which is followed by QRS (Y) In C is shown Lead II of an electrocardiogram in which the ventricular premature contraction at X gives rise by retrograde conduction to an auricular premature contraction (P) which is in turn followed by ventricular response which is supraventricular in form (Y)

Auricular Hypertrophy —Saw toothed or split P waves which may be tall or low and broad may indicate auricular hypertrophy and may result from mitral stenosis (Fig 148C)

In congenital *dextrocardia* the electrocardiogram has the following characteristics Lead I appears to be upside down and

tractions (Fig 146C) after every normal beat (3) blocked auricular premature contractions after every second beat (Fig 146D) (4) auriculoventricular premature contractions after every normal beat (Fig 146E) (5) sino auricular block every third sinus impulse being blocked (Fig 146A) and (6) block in auricular flutter alternat

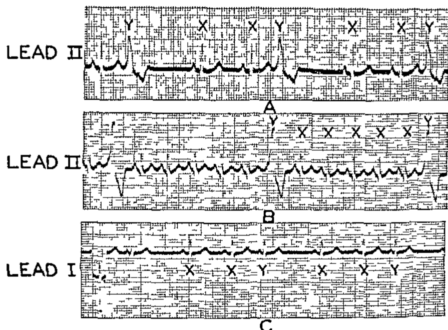


Fig 147—In A is shown Lead II illustrating trigeminy due to ventricular premature contractions (Y) after every two normal beats (X) the compensatory pause after the ventricular premature contractions making the three beats fall in a group In B is shown in Lead II ventricular premature contractions (Y) recurring after every fifth normal beat (X) In C is shown trigeminy due to auriculoventricular premature contractions (Y) occurring after every second normal beat (X) The short P R (0 08 seconds) identifies the auriculoventricular premature contractions

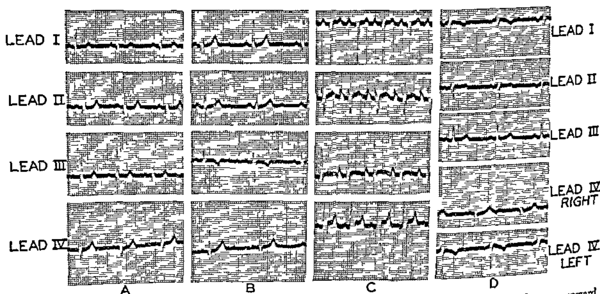


Fig 148—In A are shown four leads of normal or no axis deviation with the major QRS deflections upward in all three leads According to the Einthoven equilateral triangle amplitude of QRS = amplitude of QRS_1 plus amplitude of QRS_3 In B are shown four leads of left axis deviation QRS up in Lead I and down in Lead III In C are shown four leads of right axis deviation with QRS downward in Lead I and up in Lead III In D is shown electrocardiogram derived from congenital dextrocardia Chest Lead IV right, was taken from the right side at the P M I and Lead IV left was taken from the left side where the P M I would have been if the heart had been in the normal location it has the contour of Lead I

Leads II and III are interchanged and compared with the electrocardiogram from a normally placed heart (Fig 148D)

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CONGESTIVE HEART FAILURE

(*Myocardial Insufficiency Cardiac Decompensation*)

The association of weakness breathlessness cough abdominal discomfort swelling in the dependent portions of the body and palpitation or precordial distress together with other and less striking or less frequent phenomena makes up the syndrome called congestive heart failure Congestive heart failure is a sequel of preexisting heart disease which may result from acute rheumatic fever chronic rheumatic heart disease hypertension arteriosclerosis coronary occlusion hyperthyroidism and other less important etiologic factors While heart failure may result from a wide variety of organic diseases of the heart it may also follow some of the functional disorders such as prolonged tachycardia and auricular flutter The nature of the organic lesion sometimes influences the frequency of the appearance of one or another of these common manifestations as will be indicated in their further discussion It is important to remember however that whatever may be the underlying organic disease (or functional disorder) this train of symptoms is due to failure of the heart to maintain the normal and adequate flow of blood to the various organs and tissues The pathogenesis of the phenomena of congestive failure is presented in the section on symptomatic Manifestations of Circulatory Failure (p 1019) but it should be emphasized that venous stasis and diminished blood flow resulting in tissue and organ anoxia at present appear to be the factors of paramount significance

Clinical Manifestations —*Shortness of breath* or *dyspnea* of some degree is the

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nounced moderate or slight but are usually present Less frequently there may be palpitation, heaviness in the chest, or a sense of dull ache in the precordium

Pleural effusion is common and adds to the respiratory embarrassment by mechanical interference with pulmonary ventilation It is somewhat more frequent on the right side than on the left Not uncommonly it is bilateral The usual physical signs of fluid will be found including diminished expansion of the chest, impaired resonance, dulness, or flatness on percussion present first and always most markedly at the bases and rising often to or above the scapular angle Voice and breath sounds are impaired or absent together with impaired or absent tactile fremitus If the fluid compresses the lung there may be a zone of bronchial voice and breath sounds at its upper level and the transmitted voice may be bleating Withdrawal of fluid by needle establishes the correct diagnosis as does x ray examination by film or fluoroscope

Dependent edema results from venous stasis in the systemic circuit as contrasted to the pulmonary The slowed rate of blood flow, the increased venous pressure and often an augmented blood volume combine to promote the passage of fluid from the blood stream into the surrounding tissues There is a tendency toward retention of sodium in the tissues which contributes to retention of fluid These changes are secondary to the impairment of the circulation but may begin a vicious cycle which must be prevented or broken by therapy This edema at first may be insensible and suspected by otherwise unexplained gain in weight Puffiness of feet or ankles toward the day s end is usually the first evidence noted by the patient Since in its earlier stages cardiac edema is gravitational in distribution such ankle edema usually disappears during sleep As the amount of fluid in the tissues increases cardiac edema is found at all times in dependent tissues merely shifting in extent in response to body position

Anasarca is merely an advanced stage of edema in which the extravascular accumulation of fluid is found over most or all of the body Accompanying anasarca there is usually pleural effusion and *ascites* or free fluid in the peritoneal cavity Both pleural and peritoneal accumulations may appear before any pronounced generalized edema however and the latter may be well marked before pleural effusion or ascites has become manifest There may be some pericardial effusion but this is rarely discoverable and is not important Occasionally when right heart failure develops early, as in cases with rheumatic lesions of the tricuspid valve an asarca may appear earlier and persist for months or even years

Urinary disturbances are frequent especially a reduced daily output called *oliguria* The urine is usually concentrated specific gravity being above 1 020 and frequently contains albumen and casts of various types There is often an increase in the urates present Patients with such changes are sometimes incorrectly called 'cardiorenal cases because the urinary phenomena are generally secondary to renal functional deficiency resulting from the congestion and venous stasis These changes are reversible under therapy with digitalis and diuretics Where congestive failure results from prolonged hypertension and arteriosclerosis the vascular changes may result in nephrosclerosis In both types the blood may show some increase in the nitrogenous metabolites particularly the urea and nonprotein nitrogen (N P N) The amounts retained in uncomplicated congestive failure are usually small while they are often quite large in the presence of organic disease of the kidneys In the presence of nephrosclerosis the urine is likely to be of low and relatively fixed specific gravity as well as of large daily volume until congestive failure supervenes These are irreversible phenomena

The liver is enlarged and congested in both right sided and generalized heart failure There may be a sensation of weight or fulness in the upper abdomen and if the enlargement has developed rapidly also of pain and tenderness When *tricuspid* insufficiency functional or organic is present expansile pulsation is usually to be found Tenderness and pain occur with rapid stretching of the capsule and are absent in chronic hepatic congestion Jaundice is fairly common but usually is only slight to moderate in degree It is generally found only in the later stages and makes the outlook unfavorable

Digestive symptoms may be among the earliest complaints and at first may be the only ones They are usually vague including complaints of dyspepsia bloating fulness belching and the presence of flatus When combined with some of the foregoing such as epigastric or hypochondriac pain and tenderness they may lead to erroneous diagnosis of disease of the digestive tract liver or gallbladder

Complaints of palpitation of aching or fulness in the precordial area or of pounding in the heart chest or neck may be the only symptoms which the patient refers directly to his heart There may be a history of earlier angina pectoris or of acute myocardial infarction but symptoms of these are rarely present once congestive failure has developed The patient with auricular fibrillation may be unaware of the irregularity whereas persons often are conscious of premature systoles

Clinical Course —The course of congestive failure is variable Acute edema of the lungs may cause death in a few hours The symptoms may develop rapidly especially when induced by an intercurrent infection or by multiple pulmonary thromboses which occur relatively often in patients with mitral stenosis and terminate fatally after a few days or weeks Commonly the patient passes through successive attacks of failure often of increasing severity and duration and separated by shortening intervals of freedom from symptoms The later attacks are likely to be less and less readily controlled by treatment until the latter becomes unavailing and the patient succumbs Some patients pass through several attacks without apparent diminution of response to therapy and then begin to manifest signs of exhaustion often with cachexia and rather quickly enter a period of rapid decline to death A lobular pneumonia often terminates the course of the illness Embolism to the brain or lungs or mesenteric thrombosis may be the terminal event Some younger patients with inactive rheumatic heart disease may survive for years during which there may have been several early episodes of failure at long intervals before a progressive downhill course develops Patients with aortic lesions may die suddenly without having suffered congestive failure

Many efforts have been made to devise a satisfactory test of the functional efficiency of the heart but without great success largely because of the several extracardiac factors which may influence the results A few restricted tests deserve brief mention as of value The *vital capacity of the lungs* is reduced by the stasis and congestion resulting from failure of the left ventricle or from stenosis of the mitral valve The test is made easily with the aid of an accurate spirometer The maximal volume of air which the patient can expire in a single exhalation is expressed in relation to the surface area of the patient s body The average normal figures in liters per square meter are for men 2 61 L×M for women 2 07 L×M² The range of normal variation does not exceed 15 per cent

Venous pressure increases in congestive failure and diminishes with its relief Its determination is simple and the results may be helpful in diagnosis and in following the course of the patient s illness. Venous pressure can be estimated fairly accurately by elevation of the patient s head and torso to the level at which the external jugular vein (preferably the right) just collapses Its height above the right auricle is the level of the venous pressure This is normally between 7 and 10 cm An alternative method is the determination of the height above the auricle to which the hand must be raised to cause collapse of its distended veins Both are crude methods but give results which are helpful in routine bedside work Actual measurement may be made by a simple water manometer connected to a pelotte The height of the column required to collapse a distended vein on the back of the hand is measured with the patient s hand supported at the level of the right auricle Finally the most accurate method is that of Moritz and von Tabora This comprises the measurement of the height to which a column of saline or the blood will rise in a manometer connected with a large needle inserted into one of the antecubital veins In severe cases of failure this is often twice normal or 15–20 cm and may even exceed treble the average

The *circulation time or the velocity of blood flow* is conveniently determined by the rapid intravenous injection of some harm

less agent, the arrival of which can be detected at some predetermined point in the body Perhaps the most precise method is that of Blumgart and associates who injected Radium C into an arm vein and measured accurately the time of arrival at each of several points in the body by means of a special detector apparatus While of great value to the research student this technic is too complex for ordinary clinical use Blumgart found that arm to heart time averages 7 seconds, arm to arm time 18 seconds and pulmonary circulation time is 11 seconds in normal humans The use of other substances gives results sufficiently accurate for ordinary purposes and the technic is simple Intravenous injection of 0 6 cc of equal parts of ether and normal saline gives an arm to lung time of 4 to 8 seconds as determined by the patient s detection of ether in the expired air The observer may also detect it on the patient s breath The arm to tongue time may be measured by the development of a bitter taste following injection of 5 cc of 20 per cent solution of decholin or a sweet taste following use of saccharin With either the normal range of times is 10 to 16 seconds In congestive failure these times are prolonged while they return toward normal during recovery Other methods have been devised by Fishberg and others It should be noted that somewhat different values are given by the various methods

The *cardiac output* or *systolic output* of the heart or *minute volume* is best measured by the acetylene method of Grollman Researches with its use have added much to our understanding of the pathologic physiology of congestive failure but it is not applicable to routine clinical use because of its relative complexity The *total circulating blood volume* may be determined approximately in man by the injection and subsequent measurement of a suitable dye While the volume of the blood usually increases in congestive failure and diminishes with its control the method cannot be regarded as clinically useful because of the many factors which enter into the variations in blood volume

Each of the foregoing tests gives information concerning one or another of the circulatory phenomena associated with heart failure None provides complete information for which it is necessary to combine the data of several tests For clinical purposes they are seldom required but the physician should be familiar with the many fundamental facts learned from their use and be prepared to employ any which might be helpful in a given instance

Treatment —This rests on three major requirements lessening the burden upon the heart, increasing the efficiency of the heart and the removal of edema Three classes of drugs are of fundamental value opiates the digitalis bodies, and diuretics especially the mercurial diuretics The treatment of congestive failure is not materially influenced by the type of heart disease which has produced the failure, hence can be discussed most conveniently as an entity special variations being mentioned where necessary

Physical and mental *rest* must be imposed their degree and duration depending upon the severity and acuteness of the failure Most patients require a period of confinement to bed but some may remain ambulant if the failure is mild Because of orthopnea the patient will usually require a semi sitting position for which purpose a Gatch type of bed spring is very satisfactory Very orthopneic patients are at times better off if allowed to sleep in an easy chair with good supporting arms The patient s position should be that in which he is most comfortable The use of oxygen by means of tent face mask or nasal catheter will often relieve the patient of much distress and ease some of the burden on the heart

The *diet* should be simple readily digestible and one which does not cause gaseous distension Salt should be reduced to about 2 Gm daily in the presence of edema and spicy foods and condiments are best omitted Also when there is edema, the total fluid intake per twenty four hours should be limited to between 1 and 1.5 liters In severe edema or in anasarca the Karell diet either in its original form or somewhat modified may prove valuable The strict Karell diet consists of 200 cc of milk four times a day However aside from these possible features the matter of diet is relatively unimportant and all that is usually requisite is that the

diet be well balanced and not too abundant

Simple *laxatives are often required to prevent the patient's having to strain at stool* These include mineral oil cascara milk of magnesia and so on at times in combination *The use of a glycerin suppository or* small enema may be helpful While the bed pan is commonly employed its use by some patients is so difficult and exhausting that a *commode at the bedside is preferable* Generally a bed urinal should be required and this also permits the measuring of fluid elimination The room should be light airy *well ventilated and cheerful Visitors may* readily tire a sick person and therefore must often be restricted both in number and length of stay No visitor who upsets or *fatigues the patient should be allowed Too* often these matters are overlooked by the physician

Sedatives or *hypnotics* may be of really *great help When cough dyspnea or orthopnea* is troublesome an opiate is the most effective Doses of codeine ranging from 15 to 60 mg (gr ¼–1) may suffice but more often morphine will be required The dose lies between 10 and 20 mg (gr ⅙–⅓) and is better given hypodermically Pantopon dilaudid or other substitute may be ordered if preferred. As soon as possible the opiates should be replaced by the simple hypnotics used as required either to produce sleep or to keep the patient calm quiet and free from anxiety Those of particular value include Phenobarbital 0 015–0 1 Gm (gr ¼–1½) giving the small doses several times per day and the larger about half an hour before time for sleep Other barbiturates may be substituted in corresponding doses Chloral hydrate is often useful especially in the hypertensive patient. A dose of about 0 2–0 5 Gm (gr 3–8) usually suffices if repeated from two to four times daily Treble the larger dose may be used at bedtime to promote sleep This may be combined with the same amount of bromide Despite its disagreeable physical properties paraldehyde 4–16 cc (1 drachm–½ ounce) is a splendid hypnotic which acts promptly and does not depress the respiration or circulation It can be *administered* by mouth as the elixir (25 per cent paraldehyde) or in whiskey or on shaved ice The rectal dose is the same as the oral It may be given as an oil enema or suspended in 120–200 cc of *warm tap water and is absorbed rapidly*

Digitalis and Allied Drugs—It is essential for the physician to have accurate knowledge of these all important drugs and make *himself expert in their use All digitalis glu*cosides act directly on the heart muscle to increase the force of its contraction It has also been shown that digitalis, by direct ac*tion on heart muscle increases the efficiency* of its work that is it makes the heart work more economically Thus the digitalized muscle converts a larger amount of its *energy into external work than the undig*italized or can perform a fixed unit of work with less expenditure of energy Except for its action in some types of tachycardia and *its influence on certain abnormal rhythms* the sole indication for the use of digitalis is to control myocardial failure with signs of congestion in the pulmonary circuit (left *ventricular failure) in the systemic circuit* (right ventricular failure) or when both types are present (the common combined form of failure) The clinical phenomena *seen in the therapeutic use of digitalis de*pend upon these primary direct actions Even the slowing of the ventricular rate usually occurring in auricular fibrillation is largely the result of a direct action of the drug upon the heart and cannot be prevented or abolished by large doses of atropine which do abolish the retardation resulting from vagal stimulation The vagal action usually results from smaller doses the extravagal from larger ones bordering closely upon those which are toxic One must be familiar therefore with the common phenomena of *digitalis toxicity* These include colored vision headache nausea vomiting or diarrhea the three last being largely reflex from the heart disorders of heart mechanism such as ectopic beats auriculoventricular block and so on and changes in the electrocardiogram such as depression of the S T segment and lowering or inversion of the T waves

In the presence of congestive failure there are no contraindications to the use of digitalis It may be used safely in the presence of premature beats partial heart block hypertension and even after a recent myocardial infarction

Administration—Digitalis is best given orally in fact other modes of administration are needed only under exceptional circumstances The two preparations among the many available, which are most satisfactory for oral use are the powdered leaf and crystalline digitoxin (Digitaline Nativelle) The currently official *Pharmacopoeia* (U S P XII) requires assay of digitalis on the cat instead of the frog as the latter failed to reveal the true potency of different samples or of different galenical preparations (tinctures) when given to man U S P XI tinctures supposedly of equal potency were actually found to vary 300 per cent in strength The new U S P XII digitalis is also reduced in strength by almost a third as compared with that of U S P XI Several plans of dosage have been found satisfactory based on the average adult requirement of 1 5 to 2 0 Gm (gr 22–30) of the powdered leaf for digitalization The rapidity of digitalization should be guided by the patient s urgency of need but there is little therapeutic justification for requiring more than three to five days In nonurgent cases 0 2 Gm (gr 3) may be given three times a day for two days and then twice daily for two days after which a daily dose of 0 1–0 2 Gm (gr 1½–3) may be continued Adequate digitalization may be secured more rapidly by a descending scale of doses such as two or three doses of 0 4 Gm (gr 6) for one day and one or two on the second day followed by doses of 0 1–0 2 Gm daily Some highly skilled physicians find it wisest to administer a total of 1 5 Gm (gr 22) in divided doses within the first eighteen to twenty four hours following up with 0 1–0 2 Gm daily to maintain digitalization None of these plans is likely to cause toxic effects except rarely in susceptible persons It is wise for the physician to select the product of one manufacturer and become thoroughly expert in its use Larger single initial doses even up to the entire amount of 1.5 Gm have been given safely but they cause gastro intestinal symptoms in nearly half the patients by local irritant action The ventricular rate of patients with auricular fibrillation should be slowed to 70–90 per minute by digitalis If exercise then raises the heart rate markedly the slowing can be assumed to be vagal and additional digitalis will be needed to induce the *extravagal slowing* by which greater protection is given the heart. The use of such extra doses may induce *minor* toxic symptoms for which the physician must be on the watch Often the best therapeutic results are to be had only at this borderline level of high dosage and one must run the attendant small risks of minor intoxication Most patients who have developed congestive failure, and particularly those having auricular fibrillation will require the continued use of digitalis to maintain compensation and prevent recurrence The dose of digitalis leaf for this purpose usually lies between 0 1 Gm and 0 3 Gm per day For digitoxin it is about 0 1 mg to 0 2 mg The dose must be adjusted carefully to the needs of the particular patient but rarely falls outside the range stated Maintenance doses should be given only once daily to relieve the patient of annoyance Both digitalis leaf and digitoxin are eliminated so slowly that a uniform degree of action is well maintained by the daily ration A variety of other preparations is available for oral use but none has proved superior to these two and few are equal to them Fluid preparations are seldom required and are intensely bitter, hence often objectionable to the patient

Only about a third of the active constituents of the leaf is absorbed following its oral use Digitoxin, on the other hand is completely absorbed so that its *dose is the* same by mouth as intravenously The total dose of digitoxin by either route is 1 25 mg (gr 1/50) When there is really urgent need this amount can be given at once for the initial dose but it is wiser to divide it into fractions such as two of 0.5 mg and one of 0 25 mg given at intervals of six hours The maintenance dose is 0 1–0 2 mg (gr 1/650–1/325) During the period when larger single doses are being given the physician should observe the effects frequently enough to avoid the production of toxic symptoms by digitalis modifying or omitting further increments according to need

Rectal administration may be advisable when the drug cannot be retained because of frequent vomiting due to splanchnic congestion or because of unconsciousness The powdered leaf may be incorporated into a

suppository or one of the liquid preparations such as the tincture or injectio digitalis (U.S.P XII) may be given with a small amount of warm water as a retention enema Before either is used a small cleansing enema is desirable The dose for rectal use is the same as for oral When the nausea and vomiting have been due to congestive failure they usually will be controlled by one or two large rectal doses of digitalis so that oral administration becomes possible.

Parenteral administration is required rarely usually only by patients who are in extremis. Intravenous injection is the method of choice especially since many of the water soluble glucosides are poorly absorbed from the subcutaneous tissues and are highly irritant Ouabain appears to be the most satisfactory but others may be used if desired Intravenous digitalization must not be undertaken in a patient who has recently received digitalis in any other manner[7] The total therapeutic dose of ouabain is 1 0 mg (gr 1/60) which is best injected in fractions of 0.25 mg (gr 1/260) at intervals of one or two hours or longer The initial dose may be 0.5 mg (gr 1/130) in extreme need As ouabain is eliminated in about twenty four hours oral administration of digitalis should be started as early as possible to maintain action.

Diuretics —Digitalis causes diuresis by improving general blood flow as well as that through the kidneys This often is inadequate to eliminate edema except when it is of milder degree and diuretics must be used

One of the *xanthines* may be administered by mouth Theophylline is the most effective but is prone to cause nausea and vomiting It may be given three or four times daily in doses of 0 2–0.3 Gm (gr 3–5) for two or three consecutive days to be followed by a similar rest period without the drug Other members of the xanthine group though less effective may be better tolerated such as theobromine calcium salicylate (theocalcin) in doses of 1 0 Gm (gr 15) or theobromine sodium salicylate (diuretin) dose 1 0 Gm or theophylline ethylene diamine (aminophylline) dose 0 1–0 2 Gm All are to be given three to four times daily Urea is often much more effective than the foregoing and is not too difficult for the patient to take One may prescribe a 50 per cent solution of the pure crystalline substance, of which the patient may take from 15–45 cc (½–1½ ounces) four times per day It is best taken ice cold in chilled fruit juice particularly grape juice

The *mercurial diuretics* surpass the xanthines and urea in effectiveness and certainty of action and play a major part in the modern treatment of congestive failure. They are frequently best used from the start of treatment rather than only after other measures have been proved inadequate Employed thus they often hasten materially the recovery of the patient Their efficacy is greatest after intravenous injection The two generally accepted are mercupurin and salyrgan with theophylline The presence of theophylline in each materially reduces the local irritant action of the mercurial component if it should escape into the subcutaneous tissues or when given intramuscularly or in a suppository The dose of either is from 0.5–2 0 cc of the ampoule solution (10 per cent) The initial dose is usually 0.5 cc to test the patient for susceptibility or intolerance both of which are rare Customarily an injection of 1 or 2 cc is given every two to five days but good results may be obtained from two to three doses per day of 0.5 cc. each These smaller and more frequent doses avoid the extreme diuresis and exhaustion sometimes produced by a large single dose Frequent intravenous injections are likely to destroy the usefulness of the veins and are usually possible only in hospitals Injection should be slow The use of a fine gauge hypodermic needle is advisable both to reduce the rate of injection and to preserve the veins Diuresis begins within about two hours and has usually subsided within about eight to twelve hours As it may amount to several liters administration should take place early in the day to avoid disturbing the patient s sleep

These mercurials may be injected intramuscularly usually without too much irritation or they may be administered in the form of rectal suppositories if the patient does not have hemorrhoids They often produce troublesome rectal irritation even when the rectum is normal Their efficiency is less by these routes than by intravenous injection However the mercurial be given,

its diuretic effect often can be increased by the preceding or simultaneous administration of ammonium chloride or other acid forming salt Usually between 6–10 Gm (gr 90–150) are given per day preferably in enteric coated tablets Ammonium chloride may be given during the day preceding and on the day of the injection, or it may be used continuously for the small or moderate diuresis which it produces in many patients Thoracentesis or abdominal paracentesis may be required for removal of pleural effusion or of ascites Rarely the subcutaneous edema may have to be relieved by mechanical drainage of the legs with Southey tubes or by multiple scarification The use of such procedures particularly paracentesis of the abdomen, may be followed by a significant increase in the actions of the diuretic drugs The practice of limiting the ingestion of table salt when combined with the continued use of diuretics may lead to a depletion of the sodium reserves of the body with a resultant failure to obtain satisfactory diuresis It may then be advisable to give 5–10 Gm of sodium chloride daily for several doses to restore satisfactory elimination of edema fluid

Despite their high content of mercury the mercurial diuretics do not appear to cause renal damage even with prolonged use However they are likely to aggravate an existing nephritis It is therefore prerequisite to make certain that the albuminuria and casts are not part of a nephritis but are due solely to the renal stasis of congestive failure One should make certain that there is no albuminuric retinitis that there is no marked retention of nitrogenous metabolites in the blood, that red blood cells are absent from the freshly voided urine, and that the specific gravity of the urine is not fixed at a low level

Attacks of cardiac asthma or of acute edema of the lungs may arise and demand emergency treatment Several measures are helpful and should be employed largely in the order of their immediate availability Morphine is usually required at once (15–30 mg) given by hypodermic Atropine in doses of 1–2 mg may or may not help by reducing bronchial secretion and spasm The slow intravenous injection of 0 25–0.5 Gm of aminophylline often gives dramatic relief Oxygen, by nasal catheter, mask or tent is desirable but it often requires time to make it available According to Barach heart failure of nonrheumatic etiology responds better to oxygen inhalation than that associated with rheumatic heart disease The oxygen tent is the most comfortable method of administering oxygen, the concentration of which should be higher than 50 per cent In severe cases it may be desirable to keep the patient in an oxygen tent for a period of three to four weeks A phlebotomy of 300 to 500 cc may be most effective or a so called bloodless phlebotomy or venous trapping may suffice The intravenous injection of 50–100 cc of a 50 per cent solution of glucose or one of the other sugars such as sucrose helps occasionally Ouabain may be administered by vein or intramuscularly, followed at once by the oral administration of digitalis During the institution of these measures the patient should be kept in the orthopnea position and all possible reassurance given him

Chronic congestive failure requires the meticulous guidance of all of the patient s activities including both physical and mental activity diet, fluid and salt restriction rest and sleep In addition digitalization should be continued and the diuretics be used as required Where effective the diuretics should be given by mouth using those previously discussed Education of the patient and his family in the regulation of his activities combined with encouragement and regular clinical examinations and the foregoing treatment will usually do much to enhance his comfort and prolong his life *One should always remember that it is the patient who is being treated—not his disease*

C EGGLESTON

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ANGINAL SYNDROME

(Angina Pectoris Angina of Effort)

Definition.—The anginal syndrome is a physiologic condition characterized by chest pain which is substernal or immediately to the left of the sternum occurring in attacks precipitated chiefly by effort excitement heavy meals or exposure to cold The etiology is varied but anoxemia of the myocardium is probably the most frequent direct cause

Incidence—Although the anginal syndrome is occasionally seen in the third or fourth decade it occurs with greatest frequency after the age of forty the highest incidence being in the sixth decade The condition seems to be on the increase Whether this is apparent due to the marked reduction in infant and childhood mortality *or real is* still debatable It was formerly believed to occur with greater frequency in those whose occupations require considerable mental effort and strain but this has been shown to be untrue Men outnumber women by a ratio of at least 4 to 1 in every series of cases reported The anginal syndrome is said to be common in Jews rare in Negroes

History.—In 1772 William Heberden described a disorder of the breast" which he named angina pectoris At the time he was not aware of the association of this syndrome with cardiovascular disease for he postulated gastric ulcer as a possible cause In 1778 Edward Jenner correlated the clinical picture of angina pectoris with the autopsy findings of coronary artery disease This view was generally accepted until Allbutt, at the close of the nineteenth century put forth the hypothesis that the anginal syndrome was produced by the stretching of a diseased aorta Osler in 1898 not only held to the Jennerian view but frequently demonstrated at postmortem coronary thrombosis in patients who clinically presented the classic picture of angina pectoris Mackenzie believed that angina pectoris was *an expression of myocardial insufficiency Historically* then the anginal syndrome is usually considered as an expression of coronary artery disease The American Heart Association has clarified the situation by designating the anginal syndrome as a physiologic diagnosis

Etiology—The common factor in all cases of anginal syndrome is probably anoxemia of the heart muscle Correlation of clinical and pathologic data in coronary artery disease studies on contracting skeletal muscles in the presence of peripheral vascular disease and numerous animal experiments indicate that muscular ischemia will cause pain Mechanical and chemical irritation of the nerves supplying the heart may also play a part

Factors responsible for myocardial anoxemia may be classified as organic and functional The commonest organic conditions are as follows

1 Damage to the coronary arteries (*a*) narrowing of the lumen such as may occur from arteriosclerosis or an invasion of the wall of the artery by some infectious process for example in rheumatic fever (*b*) blocking of a coronary artery by a thrombus or embolus

2 Interference with the entrance of blood into the coronary arteries such as may occur when a syphilitic process in the aorta involves the mouths of the coronary arteries

3 Aortic insufficiency where in spite of increased demand for oxygen by a hypertropied *left ventricle the coronary blood* flow is decreased because of a low diastolic pressure

Among the functional factors may be cited

1 A very rapid heart rate *e g* in paroxysmal tachycardia where the short diastolic

period causes an inadequate coronary artery circulation

2 Marked anemia

3 General anoxemia *e g* high altitudes inadequate ventilation

The actual attack is precipitated by any cause which will put a sudden additional strain upon the heart which may increase the heart rate or blood pressure such as physical effort, mental strain or excitement systemic infections or a heavy meal

The impulses which reflexly cause the pain are conveyed to the sympathetic trunk by fibers running in the middle and inferior cardiac nerves to the corresponding cervical sympathetic ganglia and by fibers running from the posterior cardiac plexus to the upper fourth or fifth thoracic sympathetic ganglia The impulses then pass through the white rami communicantes into the spinal nerves then through the posterior spinal roots to the posterior root ganglia into the spinal cord There are however no white rami in the cervical region Therefore all pain impulses passing along the cervical cardiac nerves to the cervical ganglia must after reaching the ganglia descend along the sympathetic trunks to the upper thoracic ganglia before reaching the spinal cord A knowledge of these pathways is important for proper surgical treatment of the anginal syndrome

Symptoms—The anginal syndrome is characterized chiefly by recurrent attacks of substernal pain less frequently epigastric or precordial The pain varies in intensity and quality It may run the gamut from a slight sense of heaviness in the chest to a severe viselike crushing pain which is accompanied by a fear of impending death The duration also varies But since precipitating cause is commonly physical exertion such as climbing stairs walking against the wind excitement, or a heavy meal absolute rest usually causes the pain to subside so that the length of the attack is relatively short Occasionally attacks may come on while the patient is at rest or even when asleep There is a tendency for the pain to radiate most frequently to the left shoulder and arm and occasionally to the fingers Less frequently it may radiate to neck and jaw and teeth to the back upper abdomen or to the right shoulder At times the pain will start at one of these points before focusing on the anterior surface of the chest. Following the attack a feeling of soreness in the chest, with hypersensitive skin areas often persists for some time One of the points of radiation may show residual numbness lasting for some time after the chest pain subsides The pain is usually accompanied by shortness of breath which is also relieved by rest If the pain is referred to the epigastrium the patient will often complain of flatulence as well If the attack is not relieved by rest and lasts for an hour or more and is accompanied by symptoms of collapse, coronary thrombosis should be suspected

Physical Signs—Since the anginal syndrome is a physiologic phenomenon and the underlying causes are so diverse there are of course, no uniform objective signs Any physical signs that are present are related to the underlying cause

Diagnosis—The diagnosis is made after a careful evaluation of the history physical examination and laboratory data always bearing in mind that the characteristic anginal symptom complex is due to one of the organic or functional conditions which produce anoxemia of the heart muscle

Concerning the differential diagnosis it may be said that too often one forgets that the anginal syndrome is a purely physiologic cardiac diagnosis produced by many organic and functional factors Usually when the organic disease can be easily determined the disorder is not called the anginal syndrome but rather the name of the disease which produced the symptom complex for example coronary sclerosis or syphilitic aortitis with ostial stenosis The one important feature which is common to all conditions giving rise to this syndrome is an anoxemia of the heart muscle We must therefore differentiate the disorder from conditions which cause chest pain but do not cause myocardial anoxemia *i.e.*, extracardiac diseases such as arthritis of the left shoulder joint pleuritis pericarditis mediastinal tumors intercostal neuritis gall bladder disease and certain psychogenic disorders The psychogenic disorders most commonly confused with the anginal syndrome are neurocirculatory asthenia and anxiety hysteria In neurocirculatory asthenia (also called soldier's heart" effort

syndrome) there are general evidences of vasomotor instability namely, flushing of the face tendency to break out into profuse perspiration low blood pressure No evidence of structural heart disease is found In anxiety hysteria there is also no structural heart disease The chest pain is precordial rather than substernal There are usually pains elsewhere in the body Extreme fatigue is a prominent symptom Frequently personality changes can be detected

Prognosis —The prognosis depends upon the underlying etiologic factor The kind and amount of structural damage determines the subsequent course in those cases where the anginal syndrome is due to organic disease The individuals who have a functional basis for the disorder will probably live the normal life span

Treatment —Here again the basic treatment will depend on the cause Frequently however especially when there is structural damage no cure is possible and treatment is symptomatic in character Activity both physical and mental should be restricted to the point where the anginal syndrome is no longer produced It is a great mistake to make total invalids of patients with this syndrome because of the anxiety which may be induced by so doing Physical effort should be distributed evenly over longer periods of time so that there is never any sudden demand upon the heart

Often patients with this syndrome are *overweight* Adjustment of the diet to bring the weight to normal will help to relieve some of the load on the heart Smoking should be discouraged because of the increase in carbon monoxide in the blood and the consequent decrease of available oxygen for the heart as well as the fact that smoking will increase the heart rate and in general cause an increase in nervousness Coffee because of its action on the central nervous system will increase the heart rate and add to the patient s anxiety These deleterious effects will more than counterbalance any possible coronary vasodilatation which may occur

Drugs used for this condition can be classified under sedatives and vasodilators The sedatives act to decrease the patient s mental activities and help him to obtain restful sleep and in a measure decrease the intensity of the anginal syndrome itself Chloral hydrate or one of the longer acting barbiturates *e g* phenobarbital are usually the most satisfactory Of the vasodilators the most effective are the nitrites For immediate relief in acute attacks a nitroglycerin tablet of 0 0005 Gm placed under the tongue is used For the more severe attacks a pearl of amyl nitrite can be broken in a handkerchief and inhaled The effectiveness of the xanthines particularly aminophylline as coronary artery dilators in the anginal syndrome has not been finally established Experimental work with anoxemia or exercise tolerance tests in man appears to indicate that coronary insufficiency is less easily produced if the patient is receiving aminophylline Several clinical studies in which the results were based on the patient's report of his sensations failed to show a beneficial action In a recent review made at the request of the Council of Pharmacy and Chemistry of the American Medical Association the therapeutic claims for aminophylline and related compounds are critically analyzed The conclusions reached as to the usefulness of the xanthines in the treatment of coronary artery disease are as follows Clinical evaluation of the usefulness of the xanthines in the treatment of coronary artery disease is far from satisfactory It seems wise to place the burden of proof on those who claim therapeutic efficacy and the evidence presented so far does not seem unequivocal Alcohol in the form of whisky or brandy will often relieve the symptoms and increase the general well being of the patient

Surgical measures are used for relief only in intractable cases Several procedures are at present employed Bilateral section of the first five posterior thoracic nerve roots has been done in a relatively small number of cases Its performance requires laminectomy which in patients with advanced coronary sclerosis is not without operative risk When successfully carried through relief of pain is complete and permanent Removal of the stellate together with the second and third thoracic ganglia by the supraclavicular approach has been recommended by J C White He believes that this places less strain upon the patient than laminectomy by eliminating the necessity for the prone position and that it is more effective than excision of the stellate alone

The third procedure is nerve block by alcohol injection into the upper five thoracic sympathetic ganglia or the corresponding rami communicantes Over 50 per cent get marked relief and 12 per cent show no improvement The injection may have to be repeated after its effects wear off and the pain recurs This procedure is becoming more and more widely used as the difficulties in technic are being surmounted It is particularly valuable because there is no mortality Painful, though transient intercostal neuritis occurs in most of the cases even though the injections are skilfully made

The fourth procedure is total ablation of the thyroid gland Theoretically the aim is to lower the metabolism of the body and so relieve the work of the heart The relief of the anginal syndrome which occurs immediately after this operation is supposedly due to trauma or section of sympathetic nerves in close proximity to the thyroid gland The pain will return when the nerves function again The relief of pain which occurs in the fourth or fifth week after operation is thought to result from the lessened demands upon the heart due to the onset of hypothyroidism The postoperative management of these patients is often difficult since they must be kept constantly on a dose of thyroid extract sufficient to prevent myxedema This method is used very little at the present time

The fifth group of procedures is concerned with attempts to increase the blood supply to the heart mainly by encouraging extracardiac and intercoronary anastomoses Various types of operation have been devised In one the pectoral muscle is made adherent to the epicardial surface of the heart, in another a cardio omentopexy is performed and in still another talcum powder is placed in the pericardial sac to produce pericardial adhesions These surgical measures must be regarded as still in the experimental stage further experience will determine their value

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NEUROCIRCULATORY ASTHENIA

(Soldier s Heart Effort Syndrome Disordered Action of the Heart)

Definition —Neurocirculatory asthenia is a condition characterized by instability of the nervous and vasomotor systems with clinical manifestations of fatigue dyspnea palpitation and precordial pain

Pathology —No pathologic changes have even been demonstrated which could be ascribed to this condition

History —Because of the fact that neurocirculatory asthenia was first noted as a clinical entity in soldiers it was originally termed soldier s heart DaCosta described it during the Civil War and in World War I many cases were again reported When civilians also were shown to exhibit this syndrome the terms effort *syndrome* and disordered action of the heart were given to it Neither term is quite so descriptive of the condition as the one suggested by Oppenheimer and now in common use namely neurocirculatory asthenia

Etiology —The precise mechanism by which this syndrome is brought about is unknown Basically it is classified with the

neurasthenias that group of borderline psychic disorders wherein fatigue is prominent and the other symptoms present are referred to almost any system or organ The development of neurasthenia appears to be an hereditary characteristic In some members of the family the symptoms may be referable to the gastro intestinal tract in others to the nervous system, and still others may have the syndrome of neurocirculatory asthenia

The disease is rare at the extremes of life the greatest incidence being in young adults In civilian life the age incidence is higher than in the army Craig and White found the average age to be thirty five years There seems to be very little difference in the incidence as related to sex

Symptoms—The chief symptoms are palpitation shortness of breath precordial pain or discomfort and exhaustion The onset is frequently associated with emotional upset, anxiety or social maladjustment but may follow other conditions such as pregnancy or one of the infectious diseases The symptom of palpitation consists of a *consciousness of forceful pounding of* the heart rarely associated with an increase in heart rate Shortness of breath on effort is the symptom which prompted some observers to name this condition the effort syndrome. Again there is more the consciousness of respiratory effort than any true dyspnea Occasionally there may be a marked increase in the rate of respiration White mentions a frequent tendency to sigh as an important point in differentiating neurocirculatory asthenia from organic heart disease The precordial pain usually consists of a dull ache in the region of the left breast The pain often lasts for some time often a matter of hours There is usually no radiation and substernal pain is rare. Occasionally there may also be attacks of stabbing pain which last for only a few seconds The exhaustion *noted in nearly all* cases not only is produced by slight effort but is often unrelieved by rest

Other symptoms are faintness syncope insomnia headache dizziness increased perspiration difficulty in swallowing tremor flushing and pallor These are present in varying degrees They are evidence of instability of the vasomotor system

Physical Signs—In a typical case the patient appears anxious, the face is flushed and there is often profuse sweating at normal room temperature The respirations may be rapid Tremors are noted in pronounced cases An examination of the heart is in the main negative A forcible apex beat and some increase in the heart rate may be noted The blood pressure is usually normal but may be slightly elevated Fluoroscopic examination is negative The electrocardiogram is normal So-called functional tests' of the heart especially those based on standard exercise or vital capacity are subnormal The value of these tests in differentiating this condition from organic heart disease is thereby materially reduced

Diagnosis—The absence of signs of organic heart disease in a patient who has palpitation respiratory distress, precordial pain and fatigue should make one suspicious of neurocirculatory asthenia Further inquiry into the history will usually make the diagnosis certain Hyperthyroidism must be considered but a normal basal metabolism together with the absence of the usual signs *associated with an overactive thyroid gland* would rule it out.

Prognosis—No one ever dies of neurocirculatory asthenia On the other hand the course is usually protracted unless definite measures are taken early to correct the psychogenic factors which form the background for this condition Even then the patient may have a relapse when under some emotional strain Complete recovery can be expected in about 15 per cent improvement in 17 per cent and in the remainder the condition either remains stationary or gets progressively worse

Treatment—The only form of treatment that is in any way effective is psychotherapy The psychogenic background must be carefully explored and maladjustments corrected A plan of life free as nearly as *possible from anxiety should* then be worked out to prevent the occurrence of a relapse

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CAROTID SINUS SYNCOPE

(*Vasovagal Syncope*)

Where the common carotid artery bifurcates to form the external and internal carotid arteries there is a slight bulging which is known as the carotid sinus In this region there are in the wall of the artery specialized sensory end plates surrounded by a rich nerve plexus By means of the carotid sinus nerve which joins the glossopharyngeal nerve connection is made with the central nervous system Overactivity of the carotid sinus may cause attacks of dizziness, fainting, and sometimes convulsions The physical signs noted during the attack are a fall in arterial blood pressure and marked slowing of the heart rate Attacks may come on without any apparent cause follow an emotional upset or be induced by pressure over the carotid sinus The overactivity is usually functional without any pathologic change being noted Occasionally some organic disturbance may be responsible such as tumors in the neck pressing on the carotid sinus or a dilatation of aneurysmal proportion of the carotid artery

The *treatment* is surgical Best results are obtained if the carotid sinus nerve can be severed Stripping of the nerve plexus from the carotid artery at the bifurcation may in some cases effect a cure but in others gives only temporary relief

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DISEASES OF THE ARTERIES

ARTERIOSCLEROSIS

Arteriosclerosis leads to loss of elasticity thickening and hardening of the arteries While generally considered a process essentially degenerative and hyperplastic (Marchand Aschoff) there is much to indicate that it may be inflammatory Because of his adherence to the latter concept Virchow designated the condition 'endarteritis deformans MacCallum is of the opinion that arteriosclerosis is probably the effect of some injurious or poisonous agent upon arteries with destruction fat accumulation and repair

Pathology—For clinical purposes it is convenient to classify arteriosclerosis as follows (1) Senile arteriosclerosis atherosclerosis nodular sclerosis, (2) Monckeberg s arteriosclerosis and (3) arteriolosclerosis Although the pathologic changes in pure forms of senile arteriosclerosis and Monckeberg s sclerosis are quite distinct, no constant etiologic factor is recognized in either and the two commonly co exist The third form arteriolosclerosis, occurs almost exclusively in association with hypertension

With advancing age arteries lose elasticity This is a result of demonstrable changes in the elastic tissue of the vessel walls Associated with the elastic tissue changes the muscularis tends to atrophy and undergo fibrous tissue replacement These alterations in the vessel walls are ordinarily initiated during the fourth or fifth decade of life and when well marked constitute what is commonly called senile arteriosclerosis' The latter may produce little or no change in the size of the lumina of the vessels and therefore may lead to no significant reduction in the amount of blood supplied by them However vasomotor control in vessels thus affected is probably reduced Moreover the loss of elasticity of the larger vessels reduces their capacity as reservoirs since the ability of the arteries to store the peak work

of cardiac systole and to release it during diastole is reduced As a result, the systolic blood pressure tends to rise Thus in arterio sclerosis more work may be required of the heart for the preservation of normal blood flow and a corresponding reduction in car diac reserve may ensue Demonstrable loss of elasticity of vessels occurs as early as the third decade (Winternitz) This emphasizes the importance of the vital rubber at an early stage in the aging process

In the aorta and larger vessels the earliest macroscopic evidence of arteriosclerosis oc marked intimal lesions are generally asso ciated with less conspicuous changes in the media The atheroma eventually exhibits varying degrees of calcium deposition even bone formation Ulceration of the surface of an atheroma with discharge of its fatty con tents into the blood stream commonly oc curs The presence of such ulcers' in the intima favors thrombosis especially in the smaller vessels This variety of arterioscle rosis in which the intima is the site of maximum involvement has been called *atherosclerosis* or *nodular sclerosis* in con

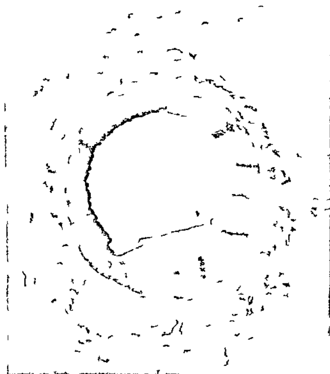


Fig 150—Senile arteriosclerosis Note the atheroma which results in narrowing of the lumen of the vessel (Courtesy of the Department of Pathology Vanderbilt University Hospital)

curs in the form of yellow streaks in the intima These are produced by the presence of newly formed connective tissue and fat ladened wandering cells As these lesions in crease in size they lead to excrescences on the intima which project into the lumen of the vessel Hyaline changes or necrosis occurs Injection specimens (Winternitz *et al*) indicate a rich network of blood vessels vasa vasorum about these lesions Thus is formed the atheroma—so called because of the soft fatty porridge like material con tained in the depth of the lesion Well tradistinction to *senile arteriosclerosis* where as we have seen the media is predominantly altered It is improbable that *any clinical distinction can be drawn be* tween senile arteriosclerosis and atheroscle rosis Indeed many pathologists consider that the two types are simply variants of the same process

It has been emphasized that the usual location of the major arteriosclerotic changes in the aorta is the intima In the arteries of the extremities the media is frequently the site of maximum involvement (Monkeberg s

sclerosis) Degeneration here frequently leads to the development of localized and sometimes encircling calcium plaques which result in palpable beads or rings along the course of the arteries Thus the brachial or femoral artery may feel like the trachea When the process is confined to the media no encroachment upon the lumen occurs and the amount of blood delivered by the vessel is affected but little if at all However in association with these characteristic

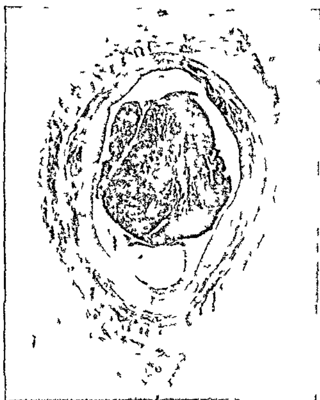


Fig 151—Monckeberg's sclerosis The major changes are in the media where atrophy of the muscularis fibrosis calcification and actual bone formation are present *Although the intima is thickened it does* not in this specimen materially reduce the size of the vessel lumen A postmortem clot is present (Courtesy of the Department of Pathology Vanderbilt University Hospital)

changes in the media in Monckeberg's sclerosis thickening of the intima frequently occurs and results in reduction in or even obliteration of the vessel lumen Arteriosclerosis of this type *is common in the peripheral* vessels of the aged and in diabetes and produces profound disturbances in the circulation of the extremities often terminating in gangrene

Arteriolosclerosis is almost invariably found at necropsy in subjects who have had hypertension Sclerosis of the larger vessels may or may not be encountered The small arteries and arterioles of the kidneys, pancreas spleen, adrenals and voluntary muscles exhibit *varying degrees of* hyaline thickening and narrowing of the lumen with changes in the muscular fibers (See Hypertension)

Clinical Manifestations—The frequency with which arteriosclerosis is associated with hypertension produces confusion and difficulty in *distinguishing between the clinical* manifestations of the two conditions It may prove useful to summarize briefly certain alterations in physiology and structure induced by arteriosclerosis (1) The reduction in elasticity of the walls of the aorta and great vessels diminishes their capacity as reservoirs vasomotor regulation is less effective the systolic blood pressure tends to rise and *additional work is required of the* heart (2) Involvement of the intima (atherosclerosis) narrows the vessel lumen and this narrowing may progress to occlusion Structures supplied by vessels thus affected respond clinically with the development of manifestations of ischemia Thus *reduction in the blood supply* to an area of the myocardium may result in angina *pectoris if the blood supply is completely* destroyed in myocardial infarction Reduction of blood supply to the kidney has been shown to produce hypertension Indeed, it appears that renal artery sclerosis may be a common etiologic factor in so called essential hypertension These are but isolated *examples of the tremendous* importance of arteriosclerosis in the production of structural *and functional changes in* all parts of the body changes due to interference with the normal blood supply (3) *Destruction of* the elastic and muscular coats produces weakness of the vessel wall thus predisposing to rupture and hemorrhage The greater the blood pressure in such vessels the more prone the vessel is to rupture

When the blood supply to various parts *of the body* is reduced sufficiently by arteriosclerosis symptoms and signs appear This *being the case it follows* that manifestations may be absent or confined to one or more areas or systems or generalized as in senility From the clinical point of view the organs which are more *commonly* affected

are heart, brain and kidneys Arteriosclerosis of the vessels of the extremities and the ab domen also produces typical clinical syn dromes

Well marked peripheral and retinal ar teriosclerosis may be demonstrable by phys ical examination, in the absence of any symptoms or signs of impairment of func tion of either these parts or of internal or gans It is a common observation that *gen eralized arteriosclerosis* may exist for long periods of time without giving rise to symp toms In time there may develop evidence that the intellectual processes are slowing etc) are usually emphasized A graceful sane mental and physical adjustment to the aging process is certainly the most desirable and practical measure to be hoped for and the physician can often do much to encour age this The tactful suggestion that the de-mands of the third and fourth decades can not be met easily by the body in its fifth and sixth decades together with the defini tion of a manner of living compatible with the patient s age is often helpful Encour agement is more important than drugs Indeed the latter are effective chiefly through suggestion Bromides and the bar



Fig 152—Arteriosclerosis Changes in the media and intima of a small pancreatic artery (a) and arteriole (b) Intimal thickening has resulted in narrowing the lumina in varying degrees Hyalinization and necrosis of the vessel walls are apparent Malignant hypertension (× 2 5 H & E Courtesy of the Department of Path-ology Vanderbilt University Hospital)

that the special senses are less acute that emotional control is less effective that car diac renal and skeletal muscle function are less efficient In short senility may ensue with its gradual reduction in efficiency of all general and special functions of the body If the aging process progresses more rapidly in one part of the body the symptoms and signs referable to that part dominate the clinical picture

The Treatment of Generalized Arterio sclerosis—There is no specific treatment for arteriosclerosis As prophylactic treat ment good hygiene and the avoidance of excesses of all kinds (food alcohol tobacco

biturates are useful when nervousness and apprehension exist but should be admin istered with care since patients with cerebral arteriosclerosis are especially susceptible to bromide and barbiturate intoxication The time honored iodides provide medicine which is usually administered by drops and taken thrice daily good attributes for a placebo The judicious use of simple analgesics and hypnotics when indicated is in order and constipation should be corrected The prob lem usually resolves itself into symptomatic treatment with due attention to the psyche Resourcefulness and optimism characterize the successful therapeutist

Heart —Arteriosclerotic disease of the heart is one of the commonest causes of death It is responsible for from 25 to 40 per cent of cases of chronic heart disease It has been observed at all ages but is com monest after fifty and increases in frequency with advancing years Men are more fre quently affected than women The symptoms and signs are those of angina pectoris dis orders of the conduction mechanism and diminished cardiac reserve or heart failure These conditions are induced by myocardial degeneration and fibrosis secondary to coro nary sclerosis or by coronary artery throm- bosis or embolism with acute myocardial ischemia Aortic insufficiency secondary to arteriosclerosis of the aorta and dilatation of the aortic ring is rare but does occur espe cially when hypertension is present The reader is referred to the special sections on the Anginal Syndrome Coronary Thrombo sis Cardiac Arrhythmias Diseases of the Myocardium and the Treatment of Cardiac Failure

The Aorta —As stated elsewhere arterio sclerosis of the root of the aorta hyperten- sion and dilatation of the aortic ring may lead to aortic valve incompetency However syphilitic disease of the root of the aorta is common and arteriosclerotic disease rela tively rare a point of importance in the eti ologic diagnosis of aortic valve incom petency Saccular aneurysms of the aorta are almost always syphilitic in origin al though arteriosclerosis may co exist (See section on Aneurysm)

Dissecting Aneurysm —In the presence of hypertension the intima of the aorta may rupture When this occurs blood extravas ates between the coats of the aorta and a dissecting aneurysm is formed Sudden agonizing thoracic or abdominal pain devel oping often during great physical exertion and followed by shock is characteristic The pain may radiate to the head back pelvic region and lower extremities and rarely to the arms In spite of varying degrees of shock even with loss of consciousness the blood pressure tends to remain elevated Evidence of arterial obstruction in branches of the aorta supplying various parts of the body especially the legs or head may de velop Moderate fever and leukocytosis occur Death usually occurs within a few hours or days from rupture of the aneurysm into the mediastinal, pleural, pericardial or peritoneal cavities Clinically, the condition is usually confused with coronary and peripheral artery occlusion The absence of electrocardiographic changes is helpful in dif ferentiating the condition from coronary oc clusion Arteriosclerosis of the aorta with atheromatous degeneration of the intima was formerly considered the cause of dissecting aneurysms However Erdheim in 1930 de scribed a rare form of cystic degeneration of the media which is generally accepted now as the commonest etiologic factor Hyperten sion is almost invariably present Athero matous ulcers may be important factors especially in dissecting aneurysms which originate in the descending aorta

The Brain —The manifestations of cere bral arteriosclerosis may be general or focal Alterations in the blood supply to the brain are brought about by arteriosclerosis through interference with normal vasomotor control of the cerebral vessels or by a gen eral narrowing of the vascular bed as a result of atherosclerosis or by actual thrombosis or hemorrhage of cerebral vessels Hyperten sion greatly favors the occurrence of cerebral hemorrhage in an individual with cerebral arteriosclerosis The reader is referred to the section on Affections of the Blood Ves sels of the Brain

Kidneys —The classic experiments of Goldblatt have focused attention on the significance of renal ischemia in the etiology of hypertension Arteriosclerosis of renal ves sels unquestionably does interfere with renal blood supply and may be found to play an important role in the production of so called essential hypertension Arteriosclerosis of the large renal vessels leads to atrophy of the parenchyma with fibrous tissue replacement (benign nephrosclerosis) Renal function usually is not impaired greatly This is in striking contrast to arteriolosclerosis of the kidney wherein the arterioles become in volved apparently as a result of hyperten sion Here serious impairment of function may occur and lead to uremia although death from cardiac failure is much more common

The Extremities —Atherosclerosis is by far the commonest cause of arterial disease of the extremities It is rare before the age

of fifty five years except in diabetes mellitus when it may appear early in life In the lower extremities obliterative lesions in the terminal branches of the posterior tibial and dorsalis pedis arteries commonly produce the earliest symptoms of the disease numbness tingling and burning sensations in the toes A sense of heaviness and pain nocturnal cramps, and weakness of the legs and feet are common complaints The foot is colder than normal and the skin may appear shiny and atrophic Faint discoloration of the toe tips may be present The pulse is feeble or absent in the posterior tibial and dorsalis pedis arteries If the process is of slow development dry gangrene may ensue, if rapid moist gangrene occurs

Intermittent claudication may develop before the signs of complete arterial occlusion are apparent. This symptom is characterized by the occurrence of severe cramping pain in the calf muscles during walking which subsides with rest The degree of exercise tolerance is determined to a nicety by the patient and continuous walking beyond this critical point is avoided The symptom is due to narrowing of the vascular bed supplying the muscles and loss of capacity to increase vascularity adequately during periods of muscular activity

Although peripheral arteriosclerosis is bilateral clinical manifestations are usually confined to the lower extremities and commonly begin on one side only The lack of pulsation in the posterior tibial and dorsalis pedis arteries is the most important diagnostic sign When the extremity is elevated it blanches promptly when placed in a dependent position color returns slowly and the veins remain collapsed for some time Arteriosclerosis must be differentiated from thrombo angiitis obliterans and from vasomotor disturbances (Raynaud s disease erythromelalgia) Arteriosclerosis rarely occurs before the fifth decade and the clinical manifestations are usually of short duration unilateral and confined to a lower extremity the vessel pulsations are faint or absent gangrene develops early the vessels can be visualized by the x ray Thrombo angiitis obliterans rarely develops after fifty occurs almost exclusively in the male and especially in the Jewish race The clinical manifestations extend over a period of years gangrene is late in development and the vessels are not demonstrable by x ray As in arteriosclerosis the lower extremities are affected symptoms at first are unilateral commonly, and the superficial arteries are usually pulseless Phlebitis and evidence of sluggish circulation may be present in superficial veins Patients with vasomotor disturbances are relatively young predominantly female, the disturbance is characteristically chronic, and gangrene develops quite late The vessels pulsate and are not demonstrable by x ray The upper extremities are predominantly affected The process is usually bilateral and manifests its presence by paroxysmal attacks

The *treatment of peripheral arteriosclerosis* is unsatisfactory The early recognition and proper management of diabetes should delay the development of arteriosclerosis in this condition High carbohydrate low fat diets are employed It should be emphasized that the control of the diabetes rather than the type of diet used appears to be the important factor Actual proof is wanting that cholesterol is an etiologic factor in arteriosclerosis in man Patients with arteriosclerotic disease of the extremities should take every precaution against trauma cold dampness and infections Prophylactic care of the feet is of the greatest importance and lists of instructions should be provided Poorly fitting shoes improper care of corns and calluses and exposure to cold and dampness are especially hazardous and predispose to infection Measures favoring the development of collateral circulation are employed Of these Buerger s postural exercises contrast baths alternate suction and pressure treatment (often called pavaex a contraction of the term passive vascular exercise) and the use of heat cradles and typhoid vaccine intravenously are of established value If definite gangrene develops amputation must be performed

The Abdomen —Although many of the digestive disturbances which occur in the aged doubtless are related directly or indirectly to the effects of arteriosclerosis upon the blood supply of the digestive organs clinical syndromes are few and ill defined The mild diabetes mellitus of the aged and the achlorhydria intestinal atony and obstipation which commonly appear late in life

doubtless are due in part to gradual impairment of the circulation

Mesenteric Thrombosis—The syndrome which develops with occlusive lesions in the mesenteric arteries resulting in infarction of the bowel, is by far the most definite clinical expression of arteriosclerosis of the abdominal vessels This is characterized by the sudden occurrence of agonizing abdominal pain usually accompanied by nausea and vomiting Exquisite tenderness and board-like rigidity of the abdominal wall rapidly develop The blood pressure and frequently the body temperature fall Abdominal distention with constipation becomes marked If bowel movements occur the stools are usually bloody In the absence of melena the clinical picture strongly suggests intestinal perforation Gangrene of the infarcted segment of bowel peritonitis and death rapidly ensue unless the affected portion of gut can be resected

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SYPHILITIC AORTITIS AND ANEURYSM

History—In the latter half of the sixteenth century Ambroise Pare remarked upon the frequent occurrence of aortic disease (aneurysm) in those who have often had the unction and sweat for the cure of the French disease The writings of Lancisi of Rome (1654–1720) and Morgagni of Padua (1761) indicate their recognition of syphilis as an etiologic factor in aortic aneurysm. Erichson credits Donald Monro 1760 with the first reference in English to syphilis as a causative factor sometimes a scorbutic or venereal taint has been accused Welch in 1875 presented data proving syphilis to be the cause of aortic aneurysm in 66 per cent of 58 cases of aneurysm found at autopsy Heller and subsequently Dohle (1895) published a description of the gross and microscopic lesions The *Treponema pallidum* was demonstrated in lymph nodes in syphilis by Schaudinn and Hoffmann in 1905 and in the wall of the aorta in syphilitic aortitis by both Reuter and Schmorl in 1907

Incidence—Cohn in a critical review of the literature bearing on the frequency of cardiovascular syphilis that is syphilitic aortitis and its complications, estimates that it constitutes from 8 to 18 per cent of all heart disease The incidence figure is lower in northern clinics serving relatively few Negro patients than in southern clinics with a large Negro clientele Figures from different parts of the United States indicate that in Negroes cardiovascular syphilis constitutes from 20 to 40 per cent of organic heart disease and in the white race from 4 to 10 per cent

While the figures furnished by pathologists indicate that aortitis is a common visceral manifestation of acquired syphilis, indeed the commonest recognized at necropsy, they do not supply the clinician with reliable information concerning the incidence of aortitis in living individuals who have syphilis It should be remembered that even when acute syphilis is untreated, about 25 per cent of patients will eventually attain a state in which no clinical or serologic evidence of the disease is manifest ("spontaneous cure") about 25 per cent will die of causes other than syphilis, about 15 per cent will have serologic (blood serum) evidence of syphilis but will remain otherwise free of sign or symptom, about 12 per cent will experience syphilis of the skin mucous membrane or bone approximately the same percentage will have cardiovascular syphilis and a slightly smaller percentage will have neurosyphilis Thus many subjects with syphilis reach the pathologist without gross changes indicative of the infection and the latter escapes detection at autopsy It is probable that the incidence of aortitis in syphilis does not exceed 10 to 12 per cent

Morbid Anatomy—Syphilitic aortitis constitutes the basic pathologic lesion—the foundation pathology—of syphilitic cardiovascular disease The changes occur most commonly in the root and arch of *the aorta*

The route traversed by the *Treponema pallidum* in its invasion of the aorta is not known The condition has not been reproduced experimentally Invasion probably occurs during the early stages of the infection when spirochetemia is known to exist the organisms penetrating the aortic wall either by direct invasion of the intima or by way of the vasa vasorum or by way of the lymphatics from mediastinal lymph nodes The location and extent of the resulting pathologic changes in the aorta are of the early death whereas more diffuse lesions of the aortic arch involve the heart but little if at all Elongation loss of elasticity and dilatation of the aorta narrowing of the orifices of the great vessels arising from the arch and aneurysm result from aortitis in the latter region

The histologic changes are those of a destructive inflammatory process In early *lesions an obliterative endarteritis of the* vasa vasorum and perivascular round cell accumulation in the adventitia are char



Fig 163.—Cardiovascular syphilis This photograph illustrates the chief manifestations of syphilitic cardiovascular disease all of which are due to syphilitic aortitis (1) Diffuse syphilitic involvement of the aorta, (2) focal aortic weakening with aneurysm formation rupture of aneurysm (3) aortic valvulitis with incompetency and left ventricular hypertrophy and dilatation (4) narrowing of the orifice of coronary arteries

Note. Extensive wrinkling, scarring and dilatation of the ascending aorta (A) a small aneurysm (B) arising from the root of the aorta the wall of the aneurysm (C) has fused with a cusp of the aortic valve (D) and has ruptured through it (at E) into the left ventricle sagging thickened incompetent aortic cusps (F) normal orifice of left coronary artery (G) partially stenosed orifice of right coronary artery (H) Marked hypertrophy and dilatation of the left ventricle is present Note thickness of ventricle wall (I) and papillary muscle (J) (Courtesy of the Department of Pathology Vanderbilt University Hospital)

greatest importance since they determine the clinical manifestations of aortitis in the individual case Thus as commonly happens involvement of the sinuses of Valsalva carries the threat of dilatation of the aortic ring or extension of the inflammatory reaction to the aortic valve with resulting incompetency or of narrowing of the orifices of the coronary arteries with embarrassment of the myocardial blood supply A relatively small area of aortitis in this locality may result in rapidly advancing heart failure and acteristic findings Probably as a result of the diminished blood supply by the vasa vasorum but possibly a direct result of the syphilitic inflammatory process degenerative changes occur in the media and in more advanced cases interruption and fragmentation of the elastic layer is conspicuous (mesaortitis ') Connective tissue replacement eventually ensues Fibrosis converts the media into merely a debris of patches of distorted muscle and elastic tissue separated by scars (MacCallum) The intima is

irregularly thickened and is frequently hyalinized These changes result in characteristic macroscopic alterations of the aorta The intima appears creased and furrowed and exhibits irregular sunken areas beneath which the wall of the aorta is actually thinner than elsewhere If the syphilitic process is fairly evenly distributed, only elongation and dilatation of the arch of the aorta may result Focal weakness of the wall may lead to aneurysm formation If the root of the aorta is involved, dilatation of the aortic ring widening and sagging of the com missures with separation of the leaflets of the aortic valve or syphilitic changes in the leaflets themselves may occur and result in aortic valve incompetency Finally narrow ing of the orifices of the coronary arteries resulting in interference with blood flow to the myocardium, may take place The fre quency with which these manifestations are encountered at necropsy is indicated in the following table

TABLE 1 SYPHILITIC AORTITIS DEPARTMENT OF PATHOLOGY VANDERBILT UNIVERSITY HOSPITAL PROFESSOR E W GOODPASTURE

Syphilitic aortitis	*Number of cases*
1 Uncomplicated	37
2 Aortic aneurysm	8
3 Aortic valve incompetency	17
4 *Aneurysm and aortic valve incompetency*	4
5 Narrowing of coronary artery ostia alone or with 3 or 4	6
Total	72

Because of the nature of the pathologic change in syphilitic aortitis the clinical manifestations of the disease fall naturally into several groups (*A*) *uncomplicated syphilitic aortitis* (*B*) syphilitic aortic insufficiency and congestive heart failure (*C*) syphilitic coronary artery disease and (*D*) *aortic aneurysm Combinations of B C* and *D* are frequent

UNCOMPLICATED SYPHILITIC AORTITIS

Symptoms—Syphilitic aortitis is rarely productive of symptoms during the first decade of acquired syphilis The average time between infections with *Treponema pallidum* and the development of symptoms of aortitis is twenty years Aortitis usu ally becomes manifest in patients who are between thirty and sixty years of age the incidence peak occurring between forty and fifty years This point is of some prac tical importance in diagnosis since rheu matic-heart disease tends to develop in younger and arteriosclerotic heart disease in older age groups Males are three times as frequently affected as females Although it is generally believed that the Negro male is more susceptible than the white male to the development of aortitis this is probably an expression of the great frequency with which syphilis occurs in the former group rather than increased racial susceptibility on the part of the Negro to syphilitic cardiovas cular involvement The frequent association of syphilitic aortitis and syphilitic involve ment of the central nervous system should be emphasized

Approximately one fourth of the cases of aortitis encountered at necropsy are latent or subclinical' That is to say the aortitis produced neither symptoms nor physical signs during life, and the patients died of some other cause The majority of these cases are examples of uncomplicated aortitis In the absence of symptoms uncomplicated syphilitic aortitis is extremely difficult to diagnose with accuracy This indicates the important role of symptomatology in the rec ognition of early cases Indeed with only few exceptions the clinical recognition of aortitis is dependent upon one or more of the fol lowing diagnostic triad (1) symptoms typical of the condition (2) signs of aneur ysm (3) signs of aortic regurgitation Thus in a consideration of uncomplicated aortitis that is aortitis which has not resulted in either aneurysm or aortic valve incom petency the history is a matter of the first importance

Approximately one half of the patients who develop syphilitic aortitis are unable to recall having had a chancre, a rash or any other manifestation of early syphilis The result of a previous Wassermann or floccula tion test may be known to the patient and thus may indicate the presence of syphilis *Substernal pain* and *paroxysmal dyspnea* are commonly referred to as characteristic symptoms in syphilitic aortitis While a sense of substernal oppression or pain is occasion ally complained of it may be and usually is entirely absent in simple aortitis When

present it is more likely due to syphilitic narrowing of a coronary orifice to aneurysm or aortic insufficiency or to unrelated hypertension and coronary disease than to uncomplicated aortitis Similarly paroxysmal dyspnea is exceedingly rare in uncomplicated aortitis (Keefer and Resnik) Its presence is almost invariably indicative of aortic insufficiency, aneurysm coronary orifice narrowing or of co existing arterial hypertension Orthopnea palpitation or other symptoms referable to the circulatory apparatus are usually absent

Physical Signs —In many instances these are entirely lacking in uncomplicated syphilitic aortitis Elongation and dilatation of the aorta may lead to increased pulsations in the suprasternal notch The carotid or radial pulse may be smaller on one side than the other as a result of narrowing of the orifices of the vessels given off by the aortic arch The pulse wave in the carotids may be exaggerated and recede quickly on account of the inelastic aorta The latter may be felt in the suprasternal notch Rarely when dilatation is great a systolic thrust and diastolic shock may be felt over the sternum Substernal dulness is increased especially to the right if the process is extensive and if considerable dilatation has occurred The auscultatory signs are few A systolic *bruit* at the aortic arch may be heard if involvement is at the root and the aortic second sound may be accentuated and characterized by an amphoric or bell like quality In the absence of arteriosclerosis and hypertension these signs over the region of the aortic valve are of considerable diagnostic importance As in senile arteriosclerosis the systolic blood pressure may be slightly elevated because of the diminished elasticity of the aorta However syphilitic aortitis is usually confined to a relatively small area in the aorta and its effect upon blood pressure is insignificant The heart is not enlarged Signs suggesting syphilitic involvement in other parts of the body may be present (Argyll Robertson pupil iritis absent patellar and Achilles tendon reflexes nodular hepatitis enlarged epitrochlear nodes gummatous skin lesions scar on penis among others)

The Wassermann reaction is positive in about 80 per cent of all cases of syphilitic aortitis The figure is somewhat lower for uncomplicated aortitis The flocculation tests yield a higher percentage of positive results Negative reactions do not exclude the diagnosis Syphilis of the central nervous system is a relatively frequent complication (approximately 15 per cent of cases) and an examination of the cerebrospinal fluid should be made in all cases The spinal fluid Wassermann may be positive when the blood Wassermann test is negative

The x ray is of great value in confirming the diagnosis in advanced cases of syphilitic aortitis In simple or uncomplicated aortitis usually it affords the clinician but little help If dilatation of the vessel especially in its ascending arch is demonstrable in a patient with syphilis uncomplicated by arteriosclerosis hypertension severe anemia or hyperthyroidism the observation warrants the diagnosis of aortitis Unfortunately this circumstance rarely obtains It is in the early uncomplicated syphilitic aortitis group that roentgenologic diagnostic aid is most needed and is in practice least reliable

Diagnosis —From the above discussion it is apparent that the diagnosis of syphilitic aortitis at the stage when the disease is uncomplicated by aortic insufficiency aneurysm or coronary artery stenosis is largely an inferential one Substernal discomfort in a man from thirty five to fifty years of age who presents a serologic or physical evidence of syphilis is very suggestive When the signs of aortic dilatation and elongation are present in such a patient in the absence of demonstrable heart disease hypertension or arteriosclerosis they are pathognomonic

Prognosis —Uncomplicated syphilitic aortitis constitutes the only genuinely hopeful aspect of syphilitic cardiovascular disease as regards prognosis The process in the aorta may become arrested spontaneously before serious damage has occurred to the aortic wall valves or orifices of the arteries It is highly probable that adequate antisyphilitic treatment usually though by no means invariably induces complete arrest of the process The co existence of hypertension renders the prognosis much less favorable

Treatment —The prophylactic treatment of syphilitic aortitis is the adequate treatment of early syphilis Moore cannot recall having seen a patient with cardiovascular syphilis who had received as many as 24 in

jections of arsphenamine for early syphilis and states that aortitis may be expected to develop in inverse ratio to the amount of treatment given for early syphilis He adds moreover, that equally satisfactory prophylactic results may be obtained by the proper treatment of latent syphilis Indeed, the rationale of treating latent syphilis rests mainly upon the protection that is thus afforded against the subsequent development of cardiovascular syphilis and neurosyphilis Of these, the former constitutes by far the greater threat

Regardless of whether the presence of uncomplicated syphilitic aortitis is merely suspected—and it should be considered a distinct possibility in any adult with so called latent' syphilis—or definitely proved intensive antisyphilitic treatment is indicated A preliminary course of from 8 to 12 weekly intramuscular injections of bismuth salicylate (0 2 Gm) together with potassium iodide by mouth (15 to 20 drops of the saturated solution thrice daily) is recommended in order to avoid the possibility of suddenly activating the syphilitic lesion with resulting congestion and edema (the Herxheimer reaction) The initiation of treatment with an arsenical is to be avoided because of this possibility Sudden deaths from occlusion of a coronary artery or rupture of a weakened aortic wall have been attributed to this rare treatment reaction On completion of the preliminary course of bismuth and iodides treatment with an arsenical is instituted Mapharsen (arsen oxide) by intravenous injection is the drug of choice The first dose should not exceed 30 mg This is increased 10 mg each treatment for three additional injections which are administered at three or four day intervals Treatment with mapharsen 60 mg twice weekly is continued until a total of twenty intravenous injections have been given (ten weeks) On completion of the first course of marpharsen antisyphilitic treatment is continued as in latent syphilis A six weeks course of weekly injections of bismuth subsalicylate intramuscularly and potassium iodide by mouth is followed by a second course of sixteen to twenty injections of mapharsen (60 mg twice weekly) It is advisable to supplement the last five weeks or the second course of mapharsen with weekly injections of bismuth subsalicylate Systematic follow up examinations with annual or biannual courses of bismuth and mapharsen are in order The Wassermann reaction is commonly irreversible in syphilitic aortitis and especially is this true when neurosyphilis is also present

H J Morgan

SYPHILITIC AORTIC INSUFFICIENCY

Since the root of the aorta at the level of the sinuses of Valsalva is the commonest location for syphilitic aortitis one would predict that involvement of the aortic valves is the commonest complication Such is the case Aortic valve incompetency is present in approximately 30 per cent of all cases of syphilitic aortitis at necropsy (24 per cent of the Vanderbilt University Hospital series) and in about 60 per cent of the cases which are recognized during life Patches of aortitis above the commissures of the valves lead to widening of the commissures with separation of the valve leaflets, extension of the process along the free border of the cusp produces thickening and contraction penetration of the cusp along the attachment to the aorta results in thickening and contraction—all lead eventually to incompetency of the valve Aortic regurgitation results in cardiac enlargement and eventually congestive heart failure, conditions rarely encountered in simple aortitis or aneurysm of the aorta uncomplicated by aortic insufficiency

Symptoms —The clinical manifestations of syphilitic aortic insufficiency and its attending cardiac embarrassment, which help to differentiate it from other forms of aortic valvular disease are (1) the development of symptoms and signs of aortic regurgitation in the third fourth and fifth decades of life later than the usual time for the development of rheumatic heart disease and before arteriosclerotic heart disease occurs commonly (2) its predilection for males and the frequency of its occurrence in Negroes (3) its rapid relentless downhill course with steadily decreasing cardiac reserve increasing cardiac enlargement congestive heart failure and death usually within three or

four years after the onset of symptoms Because left ventricular enlargement and failure develop rapidly and out of proportion to the changes in size and function of the right heart *paroxysmal dyspnea* is an impressive early symptom A sensation of *sternal pressure* is commonly complained of and frank *angina pectoris* occurs not infrequently The presence of a narrow orifice of one or both coronary arteries is always to be suspected in this connection Death often occurs suddenly It results usually from congestive heart failure coronary ostium stenosis ventricular fibrillation or intercurrent bronchopneumonia

Treatment —The nonspecific treatment of syphilitic aortic insufficiency does not differ from that of other forms of aortic insufficiency and congestive heart failure The reader is referred to the sections on chronic valvular disease and diseases of the myocardium

Experience has demonstrated that antisyphilitic treatment affords but little advantage to the majority of patients with syphilitic aortic insufficiency Nevertheless when the valvular incompetency is of recent development and when the patient is seen before cardiac decompensation has occurred specific treatment should be administered cautiously Weekly injections of bismuth together with the oral administration of iodides are recommended for from two to three months If at the end of this period the patient is in a good state of cardiac compensation injections of mapharsen beginning with 20 mg and gradually increasing to 50 or 60 mg at four to six day intervals may be employed for eight to ten weeks Sudden death may occur following an arsenical injection Nevertheless specific treatment is warranted since one occasionally encounters patients in whom the disease has become arrested apparently as the result of specific treatment The writer observed a patient who had syphilitic aortic insufficiency and two aneurysms of the thoracic aorta for a period of eight years[1] Annual courses of antisyphilitic treatment were administered during this period Death resulted from subacute bacterial endocarditis a rare complication of syphilitic valvular disease

The advent of congestive heart failure in syphilitic aortic insufficiency should preclude the use of the arsenicals with very rare exceptions In the syphilis clinic of the Vanderbilt University Hospital no antisyphilitic treatment except potassium iodide is prescribed during periods of congestive failure and only bismuth and iodides when satisfactory compensation has been restored The use of mapharsen (10–20 mg) or neoarsphenamine (0 05–0 1 Gm) in patients who have experienced congestive heart failure is confined to hospital practice and is employed only as a last resort in attempts to relieve intractable precordial pain

H J Morgan

SYPHILITIC CORONARY ARTERY DISEASE

Narrowing of the orifice of one or both coronary arteries is present in syphilitic aortitis in from 10 to 20 per cent of cases at necropsy (approximately 10 per cent of the Vanderbilt University Hospital series) and is due to localization of the syphilitic process in the sinuses of Valsalva or to the abnormally high origin of the arteries at or above the upper level of the sinuses (von Glahn) where syphilitic involvement of the aorta is common Syphilitic endarteritis in the course of the vessels is quite rare though the writer has seen it in association with a gumma of the myocardium The occlusive lesion of the orifice is of slow development and may lead to complete stenosis without producing symptoms of myocardial ischemia Scott has observed two patients in whom the heart maintained an adequate circulation certainly for days and in all probability for weeks without any blood supply through the coronary arteries Presumably collateral circulation was established through the thebesian system of vessels (Wearn) However the occurrence of precordial pain in cases of syphilitic aortitis uncomplicated or in association with aortic insufficiency strongly suggests the presence of either coronary orifice narrowing or aneurysm This is a matter of practical importance regarding treatment since injudicious use of the arsenicals in such cases may induce the Herxheimer reaction with disastrous results The discussion of the contraindications and indications for specific treatment in syphilitic aortic insuf

ficiency is appropriate here (see above) The symptomatic and supportive treatment of coronary disease is considered in the sections of this book dealing with angina pectoris and coronary thrombosis

H J MORGAN

ANEURYSMS OF THE THORACIC AORTA

Definition —An aneurysm is a sac formed as a result of focal weakness and distention of the wall of an artery A *true aneurysm* is one in which the wall of the sac is formed by at least one distended layer of the vessel wall commonly the adventitia A *false aneurysm* is produced when all of the coats of the vessel are ruptured and the blood is retained by the surrounding tissues A *traumatic aneurysm* is produced as the result of injury An *arteriovenous aneurysm* is produced by the simultaneous rupture of an artery and vein usually by bullet or knife the blood passing from artery directly to vein *Dissecting aneurysms* are produced by a linear rupture of the inner coats of the vessel blood being forced into the media or through it to the adventitia and separating the tissues of the vessel wall along its long axis (See section on *Arteriosclerosis*) *Mycotic aneurysms* form as the result of bacterial infection (streptococcic gonococcic pneumococcic etc) of the vessel wall

Aortic Aneurysm —Arteriosclerosis and hypertension in the absence of syphilis commonly produce diffuse dilatation of the aorta but rarely if ever aneurysm Pathologists agree that definite saccular aneurysms of the aorta almost invariably represent complications of syphilitic aortitis When the destructive changes in the elastic and muscle layers of the aorta which are so characteristic of syphilis are more excessive at one area of the vessel than elsewhere the blood pressure tends to balloon out the wall at that point and sacculation occurs This complication is present at necropsy in from 10 to 30 per cent of all cases of syphilitic aortitis (11 per cent of the Vanderbilt University Hospital cases) Multiple sacs may develop though this is rare Because syphilitic aortitis develops in the vast majority of instances in the thoracic rather than the abdominal portions of the vessel thoracic aortic aneurysms are over ten times as frequent as abdominal aortic aneurysms and since the segments which constitute the ascending transverse and descending arch of the aorta are the ones principally affected by syphilis, aneurysms occur here almost ten times as commonly as below the arch (Kampmeier) The condition is most frequently encountered in Negro males and in the second or third decades of syphilitic infection

Pathology —There is little that can be added to the following graphic description by MacCallum " the sac most commonly springs from the convexity of the arch and intense sclerotic alterations of the aorta surround its mouth The orifice is round or irregular in outline, and the edge is rolled over into it somewhat so as almost to overhang its cavity The cavity itself may reach a very great size the sac thus formed pushing aside the surrounding organs or embedding itself in them in the most remarkable way Mechanical effects produced in this way are of great variety depending largely upon the point of origin and size of the sac Pressure on the recurrent laryngeal nerve produces an alteration of the voice from spasm or paralysis of the vocal cord coughing dyspnea etc Pressure on the trachea flattens it and causes dyspnea Later the aneurysm may rupture into it after eroding its wall The lungs yield and collapse before the aneurysm Pressure on a bronchus narrows it and behind the obstruction bronchiectasis arises When the sac reaches the bony structures of the thorax which do not yield it hammers its way through them appearing under the skin through a hole in the ribs or sternum If it extends backward to the spine it destroys the centra of the vertebrae even down to the spinal canal leaving the yielding intervertebral discs standing almost unaltered in the same way it may break through the ribs in the back and appear under the skin there Then it is not long before the skin becomes thinned out and bluish and finally the sac ruptures so that death follows at once Often it ruptures long before reaching the skin into the pleura or pericardium trachea or esophagus or even into the superior or inferior vena cava MacCallum states

further that 'such a sac which can produce a huge and destructive tumor, which destroys itself as soon as it completes its advance is not really composed of the stretched-out walls of the vessels but [of] connective tissue and that essentially new formed the current of blood eddies *about in the cavity and its pulsation gives* the sac its power of breaking down the resistance of the tissues But the endothelial lining is imperfect and thrombosis occurs layer after layer of compact thrombus material may be hammered down on the wall of the sac *Occasionally* the aneurysm may be completely obliterated in this way

Symptoms, Physical Signs —The symptoms of thoracic aneurysm are produced by pressure of the sac upon neighboring structures thus producing interference with their function or upon the bony framework of the thoracic cage Thus a small aneurysm arising from the sinus of Valsalva may remain silent' until rupture occurs in the pericardial sac with resulting hemopericardium and cardiac tamponade or if the sac points anteriorly it may rupture into the pulmonary artery Aneurysms arising from the aorta in the region between the aortic valve and the innominate artery (the ascending arch) may attain great size without producing symptoms Here the sac tends to point up*ward forward* and to the right *Physical* signs may be abundant (the aneurysm of signs) Proximity to the anterior chest wall results in visible pulsations in the suprasternal notch and pulsations of the upper sternum and upper right interspaces with or without an actual expansile bulging in these regions The heart may be displaced downward and to the left and substernal dulness increased to the right over the region of the sac Compression or traction on the innominate artery results in a demonstrable diminution in the size of the pulse in the right carotid subclavian brachial and radial arteries and lowering of the blood pressure in the right arm A systolic thrill and diastolic shock are usually palpable over such aneurysms and on auscultation a rough systolic murmur followed by a snapping sound coincident with closure of the aortic valve (if not incompetent) may be heard Aneurysms rising from this region may point posteriorly or attain enormous *size and* compress *the right bronchus* or lung (resulting in atelectasis) compress and deflect the trachea (dyspnea tracheal tug) compress the superior vena cava (venous stasis, cyanosis) recurrent laryngeal nerve (hoarseness brassy cough) *esophagus (dysphagia) and sympathetic* ganglia (anisocoria unilateral sweating) These manifestations however are much more likely to develop when the sac arises from the transverse portions of the arch (Broadbent s Aneurysm of Symptoms) Aneurysms below the arch in that part of the aorta extending from the level of the sixth to the twelfth dorsal vertebrae are rare frequently nonproductive of either symptoms (unless spinal nerve roots are compressed) or physical signs and are usually discovered only by x ray examination or at necropsy In large aneurysms of the transverse and descending portions of the arch pulsations may be visible in the left interscapular region

Aneurysms rarely develop in patients with syphilitic aortitis already complicated by the presence of syphilitic aortic insufficiency Whether this is due to the short duration of life of patients with the latter complication or to the protection afforded the weakened aortic wall by the low diastolic blood pressure which is associated with aortic re*gurgitation is not clear* The presence of aneurysm however is no protection against the subsequent development of syphilitic aortic insufficiency Narrowing of the orifices of the coronary arteries occurs in about one fifth of the cases and coronary sclerosis unrelated to syphilis may be present Syphilitic aortitis with aneurysm which is uncomplicated by aortic valve or coronary orifice involvement does not produce cardiac enlargement or congestive heart failure Under these circumstances cardiac enlargement if present is almost invariably due to co existing hypertensive arteriosclerotic or rheumatic heart disease

Pain dyspnea and cough are the commonest symptoms of thoracic aneurysm The former occurred in 65 per cent of Kampmeier s series of 596 cases It may consist merely of *a persistent sense of substernal* discomfort The latter may be referred to the neck shoulder or back and sometimes

undergoes periodic intensification of great severity Bone erosion may produce boring agonizing pain which is almost intolerable, or may be painless A striking feature is that certain positions assumed by the patient may cause intensification of pain or afford relief True angina pectoris, occurring either at rest or after exertion and relieved by nitroglycerin occurs with approximately the same frequency that coronary disease is encountered at autopsy *Dyspnea* is complained of almost as commonly as pain When bronchial or tracheal *compression* is present it may be continuous and associated with inspiratory stridor In the absence of pressure on the air passages and aortic insufficiency dyspnea is rarely present When aortic insufficiency complicates the condition paroxysmal dyspnea and frank attacks of acute pulmonary edema are not uncommon *Cough* often of a brassy" character is an important symptom in almost half of the cases It is the result of either recurrent laryngeal nerve tracheal or bronchial pressure or in patients with aortic insufficiency congestive heart failure

X ray —Except in the case of infrequent small sacculations of the aorta which are situated in such positions that they cannot be brought into profile and made a part of the aortic silhouette roentgenology is of inestimable diagnostic value Fluoroscopic examination by an expert with visualization of various profiles of the aortic shadow and confirmatory roentgenograms are usually though not always diagnostic when interpreted in the light of a careful bedside study

Prognosis —The average time which elapsed from onset of symptoms to death in Kampmeier s series was seven to eight months Extremely rare cases are recorded in which the aneurysmal sacs became obliterated by laminated clots which subsequently organized Even calcification may occur Such patients may live many years

Diagnosis — Silent' aneurysms are discovered usually by an x ray examination of the chest or at necropsy When productive of either symptoms or physical signs the condition must be differentiated from other mediastinal or thoracic tumors Neoplasms are not apt to erode bone and may be associated with superficial lymphadenopathy cachexia and anemia The following points may be emphasized in the differentiation of aneurysm from mediastinal neoplasm (1) The *history* of syphilis or serologic or physical evidence of its presence (aortic regurgitation, Argyll Robertson pupils absent knee or ankle jerks superficial gummata or scars gumma of liver etc) (2) the presence of a mediastinal tumor which, regardless of the '*neighborhood*" pressure symptoms and signs is demonstrably expansile by physical examination (pulsations in chest walls systolic thrill and murmur, diastolic shock and accentuated second sound or tracheal tug) (3) expert roentgenologic examination Tuberculosis may be suggested by the pulmonary signs resulting from bronchial or lung compression Fever and tubercle bacilli in the sputum are absent and x ray examination usually dispels all doubt as to the true nature of the condition

Treatment —The treatment of thoracic aneurysms is essentially symptomatic Complete bed rest often affords great relief from pain dyspnea and cough The iodides have a strikingly beneficial effect upon the pain of aneurysms Fifteen to 20 drops of the saturated solution of potassium iodide thrice daily is sufficient Nitroglycerin or amyl nitrite is indicated for angina pectoris Morphine should be used freely for its analgesic and soporific effects The barbiturates are helpful in reducing the amount of morphine required but there is no justification for withholding the latter drug

If aortic insufficiency and congestive heart failure are not present patients with aneurysms should be given the benefit of antisyphilitic treatment Moore s results are so encouraging that one questions the presence of actual sacculation in all of his patients Nevertheless there is but little to lose and possibly much to gain by the institution of cautious antisyphilitic therapy The reader is referred to the discussion of the treatment of syphilitic aortitis complicated by syphilitic aortic insufficiency

HUGH J MORGAN

ABDOMINAL ANEURYSMS

Abdominal aneurysms are rare In asthenic patients with thin abdominal walls the normal aorta can be palpated readily A definitely expansile tumor along the course

of the aorta the upper and lower limits of which are clearly definable by palpation is rarely encountered Excruciating boring abdominal pain is the characteristic manifestation of abdominal aneurysms and this is usually due to erosion of the bodies of the lumbar vertebrae The blood pressure *in the legs may be reduced to a figure* equal to or lower than in the arms In three fourths of the cases radiographic demonstration of eroded bodies of lumbar vertebrae is pos*sible and this is of great* diagnostic assistance Rupture of the aneurysm may occur into the peritoneal cavity or retroperitoneal spaces and, less frequently into the gastro intestinal tract The attending shock and abdominal rigidity may result in a condition suggesting perforation of a hollow viscus

DISSECTING ANEURYSMS

These are discussed in the Chapter on Arteriosclerosis (p 1164)

HUGH J MORGAN

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DISEASES OF THE PERIPHERAL VESSELS

GENERAL CONSIDERATIONS

By usage the term peripheral vascular disease is limited to conditions in which blood flow through the extremities is disturbed by structural or functional abnormality of the peripheral blood vessels In many instances however the primary cause of the disorder is neither peripheral nor vascular as illustrated by some cases of spasmodic cyanosis of the fingers which though closely resembling Raynaud's disease may be caused by such distant lesions as spondylitis or cervical rib Furthermore a great variety of systemic disorders occasionally exert striking effects on peripheral blood flow In this group are such unrelated conditions as the anemias polycythemia vera hyperthyroidism myxedema and of course cardiac disease

In elderly patients pain and indolent ulcers involving the digits may be the initial symptoms of widespread arteriosclerosis of which the peripheral vascular disease is only a part It is true that the extremities are richly supplied with arteriovenous anastomoses but the hands and feet are so frequently exposed to varying temperature and to trauma that the digits are likely to be the first parts to suffer when general vascular disease impairs the efficiency of the circulatory system as a whole For correct diagnosis and efficient therapy one must remember that blood flow to any part depends not only upon the state of the local vessels but also upon the functional adequacy of the general circulation and the influence of the sympathetic nervous system

Vasodilatation, Vasoconstriction and Vasospasm —Normal peripheral blood vessels dilate in response to local heat muscular activity local injury increasing blood volume interruption of sympathetic vaso constrictor impulses warming of the other extremities or of the body vasodilator drugs and injection of pyrogenic substances such as typhoid vaccine Organic arterial disease prevents the affected vessels from dilating fully in response to these agents

Peripheral vasoconstriction results from local cooling chilling of the body decreased blood volume irritation of peripheral nerves and the action of certain drugs Vasoconstriction which is abnormally complete or prolonged is termed *vasospasm* or *angiospasm* This excessive and unphysiologic vasoconstriction sometimes affects structurally normal vessels as in early Raynaud s disease but is frequently secondary to organic arterial disease especially embolism and thrombo angiitis obliterans Severe ar

terial spasm may also accompany acute thrombophlebitis

Excessive dilatation of structurally normal vessels is rare and occurs only in erythromelalgia Prominence of the peripheral veins or capillaries is usually due to structural disease which produces either mechanical distention as in arteriovenous fistula or asphyxial relaxation as in various types of arterial occlusion

The Symptoms and Signs of Peripheral Ischemia—The vast majority of patients with peripheral vascular disease suffer from the effects of ischemia concerning which certain simplifying general principles may be mentioned After routine history and examination have been completed a few additional observations will detect first inadequacy of peripheral blood flow and second its degree and type, whether due to simple vasospasm or to organic arterial disease

Coldness of the extremities signifies decreased blood flow and is normal or abnormal depending on the circumstances under which it occurs Skin temperatures vary widely even in health since body heat is in large part conserved or dissipated by cutaneous vasoconstriction or vasodilatation respectively Temporary coldness of the extremities may be normal but severe and persistent coldness is abnormal Single uncontrolled skin temperature readings are therefore, often misleading whereas differences in the temperatures of corresponding parts of two symmetrical limbs similarly treated and exposed are more significant In the absence of disuse atrophy and diseases of the nervous system unilateral coldness is generally due to structural disease of the corresponding blood vessels Exceptionally however the more grossly diseased limb will be warmer apparently because circulation is largely maintained by superficially placed collateral channels which are relatively insensitive to vasoconstrictor impulses

Intermittent claudication refers to aching or constricting pain which may arise during activity of any group of muscles but most typically affects the calf muscles The pain appears gradually after a relatively constant amount of exercise and is promptly relieved by rest If exercise is continued in spite of pain the affected muscles become spastic and cramps may occur In the absence of general anemia intermittent claudication bespeaks structural arterial disease Advance or quiescence of local vascular disease is reflected by gradual diminution or increase of exercise tolerance which can be measured by controlled pacing or by some type of recording ergometer

Rest pain accompanies (1) sudden arterial occlusion by thrombosis or embolism (2) indolent ulceration, gangrene or other advanced trophic changes and (3) ischemic neuritis In contrast to intermittent claudication it is not relieved by rest and is usually worse at night Patients often discover that they can relieve this agonizing pain somewhat by gently massaging the skin near lesions or by hanging the extremity over the side of the bed

Skin color depends first upon the number and fulness of the capillaries and subpapillary venules second upon the composition of the venous blood with reference to the number of erythrocytes and their oxygen saturation Arterial blood normally enters the skin rapidly enough to prevent conspicuous blanching of the digits even when the extremities of the recumbent patient are raised well above heart level If general anemia be absent *conspicuous pallor* of the elevated extremities suggests but does not prove the existence of organic arterial occlusion *Cyanosis* limited to the extremities indicates that the minute vessels are filled with excessively deoxygenated blood resulting either from venous stasis or from slow arterial inflow

In a cold limb pallor and cyanosis may be due wholly to vasospasm the vessels still being capable of dilating widely under proper conditions Vasospasm can be abolished by warming the limb in a water bath at 35° to 40° C for twenty minutes after which either pallor on elevation or cyanosis in dependency provides strong presumptive evidence that the arteries are organically diseased

Rubor a persistent red or reddish blue discoloration of the cold extremity appears when the cutaneous capillaries and venules are permanently dilated owing to injury from persistent anoxemia cold or low grade inflammation Moderate redness is normal in a naturally warm extremity However peripheral blood flow may be exaggerated

though skin color is still normal since blood flow and skin temperature depend chiefly on arteriolar tone while skin color varies with the tone of the minute vessels

Trophic changes in the skin accompany nearly all slowly developing peripheral vascular conditions and indicate merely that ischemia is severe or has been so at intervals The subcutaneous tissues ordinarily meager may at first be puffy and thickened Later the skin becomes dry atrophic shiny tightly drawn and subject to indolent ulceration The nails become hard brittle ridged and otherwise deformed The severity of trophic manifestations corresponds so closely to fluctuations in the adequacy of peripheral circulation that there is no need to invoke the activity of so-called trophic nerve impulses '

Diminished pulsation of the peripheral arteries is detected with the fingertip or with the oscillometer the latter serving especially to determine the point at which pulsation ceases in the thigh or calf where the vessels are too deep to be palpated The instrument is more reliable in demonstrating relative differences between the deep pulses of two symmetrical limbs than in measuring absolute deviations from normal A pulse not palpable in the cold extremity may appear when vasoconstrictor tone is diminished by heat since vasospasm occasionally obliterates pulsation in arteries still able to dilate Peripheral pulses may be obliterated by aneurysm or coarctation of the aorta while arterial anomalies may be responsible for failure to feel pulsation in the usual situations A normal pulse is sometimes felt at the wrist or ankle while the smaller distal arteries and arterioles are occluded by advanced organic disease

Indolent ulceration and *gangrene* indicate conspicuous or complete local ischemia The vessels in and near the lesion are commonly thrombosed while other vessels in the extremity usually show organic disease but may be structurally normal if the underlying condition is essentially vasospastic The occurrence of local gangrene and ulceration renders it likely that widespread organic arterial occlusion is present but does not justify this diagnosis unless other evidence of widely distributed structural disease is found

Tests for Differentiating Vasospasm and Structural (Organic or Occlusive) Arterial Disease—The degree to which peripheral ischemia is due (1) to pure vasospasm or (2) to organic arterial disease can be determined by *observing the rise of digital skin temperature* which follows temporary abolition of vasoconstrictor tone in the extremities The patient thinly clad lies with the extremities exposed to room air at a temperature between 18° and 21° C When the digits have cooled sufficiently, vasoconstrictor tone in the extremities is abolished by one of the following procedures

1 Injection of procaine around appropriate sympathetic ganglia

2 Anesthetization by procaine of appropriate peripheral mixed nerves

3 Spinal anesthesia (for lower limbs only)

4 General anesthesia

5 Raising body temperature by (*a*) enclosing body (excepting limbs under observation) in an electric heat cabinet (*b*) immersing two uninvolved limbs in water baths at 42° to 44° C for thirty five minutes

As soon as vasoconstrictor impulses are removed from the extremity normal vessels dilate peripheral blood flow increases and digital skin temperature rises rapidly to the normal vasodilatation level between 30.5° and 33° C Such a normal vasodilator response indicates that the peripheral arteries are able to dilate fully and that significant organic arterial disease is absent A partial vasodilator response *i e* rise of digital skin temperature to between 27° and 29 C indicates that moderate organic vascular disease is present in the area studied If skin temperature fails to rise or actually diminishes during the procedure the vasodilator response is absent indicating advanced occlusive disease locally The capacity for vasodilatation has been measured also by observing changes in skin temperature after the intravenous injection of typhoid vaccine (vasomotor index) This procedure should not be used in studying arteriosclerotic patients because of the danger of producing thrombosis The temperature standards of the vasomotor index differ from those of the tests listed above

For studying the upper extremities body warming is the simplest and most reliable method For the lower extremities body warming is generally satisfactory but occasionally fails to release extreme vasospasm, under these conditions anesthetization of the posterior tibial nerves or spinal anesthesia is more reliable

To determine how far upward in the extremity organic occlusion extends other procedures must be used viz (1) the oscillometer (2) histamine puncture (3) reactive hyperemia and possibly (4) arteriography The limitations of the oscillometer have been mentioned Histamine (1 1000) punctured into the skin of the warm horizontally placed extremity normally produces a wheal and hyperemic flares in five minutes or less (Starr) If a wheal fails to appear within five minutes it can be concluded that blood flow is diminished in that skin area Reactive hyperemia (Pickering) is produced by arresting blood flow completely for five minutes after the extremity has been warmed and emptied of blood Sudden release of circulation is followed by a brilliant hyperemic flush which normally reaches the tips of the digits in less than five seconds If organic occlusion is present the flush is delayed and faint Compression of diseased arteries and local arrest of circulation incur some risk of inducing thrombosis

Arteriography involves roentgenography after intra arterial injection of radiopaque solutions This procedure reveals the site and nature of anatomic changes in the peripheral vessels as well as the size and number of collateral channels Arteriography is sometimes painful and is at present contraindicated in active vascular disease owing to the danger of producing thrombosis

Vasodilator Drugs —In treating peripheral vascular disease prolonged vasodilatation is required so that the evanescent effects of amyl nitrite nitroglycerin and acetylcholine are generally of little therapeutic value The efficacy of those drugs which have prolonged vasodilator action depends upon the grade of vasospasm to be overcome and the degree to which structural disease has rendered the peripheral arteries rigid and incapable of dilatation In addition vasodilator drugs often lower systemic blood pressure so that in many cases particularly with structural disease though vasodilatation is obtained peripheral blood flow is increased but little Nevertheless appropriate vasodilator drugs should be tried in all cases because their action though often feeble and capricious is sometimes strikingly effective even under adverse conditions

Ethyl alcohol given in the form of acceptable beverages to provide 0.5 cc alcohol per kilo body weight induces peripheral vasodilatation which lasts on the average for four hours Acetyl β methylcholine should be given orally in doses of 0 1 to 0.5 Gm., and repeated as necessary Undesirably intense side effects can be terminated promptly by injecting atropine Papaverine hydrochloride may be given orally or subcutaneously (0 03–0 06 Gm) and intravenous adminis

DISEASES OF THE PERIPHERAL ARTERIES

Primarily vasomotor (functional) conditions	Vasoconstrictor	1 Acrocyanosis 2 Raynaud s disease (primary) Secondary Raynaud s phenomenon as in scleroderma neurological disorders crutch trauma etc
	Vasodilator	3 Erythromelalgia (primary) *Secondary vasodilator conditions erythralgia*
Primarily organic (structural) conditions	Ischemic (occlusive)	Inflammatory 4 Thrombo angiitis obliterans 5 *Ergotism* 6 Periarteritis nodosa 7 Arteritis in systemic infections Degenerative 8 Arteriosclerosis simple and diabetic Traumatic (with regard to peripheral vessels) 9 Embolism 10 Frost bite Caustics phenol
	Hyperemic	11 Glomangioma 12 Arteriovenous fistula

tration (0 01–0 03 Gm) at intervals of three to four hours has been recommended for relaxing vasospasm in embolism Theophylline ethylene diamine (orally 0 09 Gm three times daily) and theobromine sodio salicylate (orally 0.5–1 Gm three times daily) are said to be helpful in certain vasospastic cases of thrombo angiitis obliterans and arteriosclerosis though useless in Raynaud s disease Thyroid substance in dosage controlled by frequent estimations of basal metabolism is often very useful especially if basal metabolism is low initially

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ACROCYANOSIS

Acrocyanosis (Crocq 1896 chronic acro asphyxia Cassirer 1900) is a somewhat indefinite type of mottled peripheral cyanosis which is induced or accentuated by cold and which affects the hands and feet symmetrically with few or no symptoms and no serious consequences

This condition the etiology of which is unknown is primarily vasospastic involving chiefly the smaller arterioles of the skin The cutaneous capillary loops are numerous and tortuous Through large venous limbs they connect with a rich dilated subpapillary venous plexus When vasoconstrictor tone is abolished the peripheral vessels dilate to the normal degree though sometimes rather slowly

Acrocyanosis occurs in men and women especially the latter without special age incidence It may develop suddenly in asthenic individuals at puberty or gradually in later years particularly in those whose work requires prolonged exposure to cold Acrocyanosis may also be associated with the effort syndrome chronic diseases such as arthritis or various neurologic disorders Association with acromegaly and ovarian dysfunction has led to the suggestion that acrocyanosis is merely a symptom of endocrine imbalance

The unevenly mottled blue and red discoloration of the skin extends from a line above the wrists and ankles to the digits increasing in degree distally The cyanosis is intensified by cold or emotion and relieved by warmth The digits are habitually cold and sweat profusely but the soft tissues are normal or at most puffy Hypesthesia of mild grade may be present The course of acrocyanosis is entirely benign since no lesions have developed in patients followed over years The associated hyperhidrosis may however require therapy

Acrocyanosis is easily differentiated from various types of generalized cyanosis because the discoloration is limited to the hands or feet and disappears when the extremities are warmed Acrocyanosis can be distinguished from Raynaud s disease by the type of discoloration and by the absence of even slight pain In acrocyanosis histamine puncture produces a brilliant flare and conspicuous wheal in the cyanotic digits In Raynaud s disease histamine produces neither hyperemic flare nor wheal in the digits *during a paroxysm of cyanosis*

Except for reassurance treatment is usually unnecessary Possible endocrinal abnormalities should be investigated For cosmetic reasons the condition may be made less conspicuous by local protection from cold wearing of warm clothing vasodilator drugs (see p 1178) thyroid substance contrast baths and lotions for hyperhidrosis Carbon dioxide saline baths have been recommended Sympathetic ganglionectomy or preganglionic sympathectomy has been used but the trivial nature of the condition rarely if ever warrants surgical treatment The alcoholic injection of paravertebral sympathetic ganglia has in skilled hands relieved distressing hyperhidrosis

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RAYNAUD S DISEASE

Raynaud s disease (Raynaud 1862) is the primary or idiopathic form of paroxysmal, bilateral cyanosis of the digits with or without local gangrene The attacks of cyanosis are produced by cold or emotion and relieved by heat

Etiology and Incidence —The etiology of Raynaud s disease is unknown although constitutional predisposition may be a factor Familial incidence has been described nationality plays no role Women who are underweight asthenic and subject to mental stress are most frequently affected Occurring at any age it is less common before puberty and after forty without relation to menopause or irregular menses Men are affected but so rarely that the essential diagnostic criteria mentioned below should be considered minutely before making the diagnosis in a male Secondary forms of vasospasm are more equally distributed between the sexes True Raynaud s disease occurs on the average once in 3000 general medical cases and once in twenty to twenty five peripheral vascular cases

Pathologic Physiology —The paroxysmal cyanosis of the digits is due to complete interruption of local blood flow by tight constriction of the digital and palmar or plantar arteries Pallor when it occurs spontaneously indicates that the minute cutaneous vessels are sharing in the vasospasm Raynaud in his original descriptions (1862 1874), concluded that excessive vasoconstrictor tone of central origin must be responsible In more advanced cases the involved vessels are also abnormally reactive to cold (Lewis) Typical attacks of digital cyanosis can then be produced simply by immersing the affected extremities for twenty minutes in water at *15° to 18* C

As the attack begins capillary blood flow ceases and capillary pressure falls below normal The digital capillaries, at first small eventually widen and become strikingly saccular or aneurysmal but the intensely cyanotic blood remains stationary and the skin cold As arterial spasm relaxes spontaneously or in response to heat skin color changes from blue to red, blood flow becomes rapid surface temperature rises and capillary blood pressure increases well above normal This reactive hyperemia subsides and circulation remains normal until the next paroxysm of vasospasm is induced

In the early stages of the disease the arteries, large and small are histologically normal Later, in progressive cases the intima is thickened and the muscular coat of the arteries hypertrophied Eventually thrombosis of small arteries in the digits leads to focal gangrene although elsewhere the arteries are still histologically normal or show only slight hypertrophy Pathologic changes in the sympathetic ganglia although described occasionally are not characteristic or uniform

Symptoms and Signs —The onset is usually gradual the first mild attacks appearing in winter or, less commonly during a period of emotional stress Initially attacks may be unilateral but they soon become bilateral and are induced regularly by emotion or by exposure of the body or digits, or both to cold Infections fatigue and nervous exhaustion increase their frequency and severity In a typical well developed attack from one to four digits (thumb often excepted) on each hand become deeply blue or initially white then blue The digits are affected to different levels and the terminal phalanges most severely The fingers are cold more or less numb and may be covered with perspiration Prolonged cyanosis is accompanied by aching pain and awkwardness in fine movements The attacks end spontaneously or can be terminated at any time by immersing the hands in warm water or by going into a warm room During recovery the cyanotic areas are gradually invaded by tongues of reactive *hyperemia* which extend slowly or rapidly until the affected digits are brilliantly red throughout If recovery is slow pallor cyanosis and hyperemia may *co exist in adjacent* patches of skin Tingling throbbing slight swelling and rising skin temperature accompany the rapid return of arterial blood flow Depending on the se

verity of the condition attacks may be rare or they may occur many times per day between attacks the digits appear normal or in severe cases remain mildly cyanotic The attacks may disappear entirely during pregnancy

The hands alone are affected in half the cases hands and feet in the remainder nose cheeks ears and chin are involved much more rarely The course of the disease varies after onset it may persist indefinitely in mild form or improve spontaneously Approximately one third of the cases are progressive the attacks become more numerous persist during summer last longer and disappear less completely until mild cyanosis is more or less constantly present The vasodilator response is usually still normal or *very slightly reduced*

Trophic changes appear in progressive cases usually one to four years after onset The *fingers become thin and tapering* their skin smooth shiny, less mobile and eventually tightly stretched (sclerodactyly) The nails grow slowly and are ridged or curved Recurrent infections and small areas of local cutaneous gangrene appear on the fingertips but gangrene of a whole digit is rare Minute scales of necrotic tissue separate slowly and painfully leaving tiny depressed scars or pits At this stage the abolition of vasoconstrictor tone produces a vasodilator *response which is slow and incomplete* in the more involved digits but usually normal in the others

Prognosis.—Mild grades of Raynaud s disease improve slowly or remain stationary for years and the attacks being few and avoidable are merely an inconvenience The progressive form with recurring infection and local gangrene becomes increasingly painful and disabling though only rarely is more than the distal phalanx lost Generalized scleroderma and atrophic arthritis, which are not infrequently associated with progressive Raynaud s disease may produce extreme deformity and disability

Diagnosis.—The essential diagnostic criteria are (1) digital pallor or cyanosis occurring in intermittent attacks induced by cold or emotion and followed by recovery with the redness of reactive hyperemia (2) symmetric or bilateral involvement of digits, (3) absence of occlusive arterial disease or, at most, in progressive cases mild involvement of the digital arteries (4) gangrene if present usually limited to small areas of skin (5) conspicuously greater incidence in females than in males (10 to 1), (6) absence of any disease or anatomic abnormality to which paroxysmal digital cyanosis might be secondary

Paroxysmal digital cyanosis, or Raynaud s phenomenon of the secondary type occurs with thrombo angiitis obliterans arteriosclerosis (dead finger) crutch trauma pneumatic hammer disease cervical rib and disseminated lupus erythematosus More or less typical Raynaud s phenomenon may occur secondarily in *diseases of the central nervous system* osteoarthritis of the spine traumatic arthritis with painful osteoporosis *spina bifida neuritis causalgia and poisoning* by arsenic or certain heavy metals Spasmodic digital cyanosis hemoglobinuria and *urticaria from cold occasionally occur together* in congenital syphilis

Bilateral gangrene of the digits (Lewis) appears suddenly in children or young adults without previous attacks of discoloration and without exposure to cold The fingers toes nose and ears become permanently cyanotic and within a few days gangrene develops in the distal phalanges of one or more fingers often symmetrically and bilaterally Cyclic color changes of the Raynaud *type first appear during the stage of* healing This syndrome should not be termed fulminant Raynaud s disease since gangrene is extensive and due to sudden thrombotic occlusion of the final end branches of the digital arteries Raynaud s phenomenon has also been observed *after* massive gangrene occurring in malnutrition and during certain *infections e g* typhoid fever typhus pneumonia influenza and streptococcic sore throat

Simple disuse of an *extremity paralysis* and section of mixed nerves eventually produce coldness of the affected parts with vasoconstriction but not the cyclic color changes of Raynaud s disease Some normal subjects at or before puberty observe incomplete cyanosis or pallor of one or two digits (dead finger) after exposure to cold or rarely after emotional disturbance No necrosis or trophic changes are observed and the attacks disappear within a few

years There is no reason to regard this mild form of vasospasm as a prodromal stage of Raynaud's disease

Treatment—Mild cases with infrequent slight attacks limited to the winter months and without trophic changes or gangrene, may be relieved by high caloric diets relax ing mental stress wearing heavier clothing protecting the extremities whenever ex posure to cold cannot be avoided and mov ing to a warm climate Smoking has been *shown to produce vasoconstriction and the* use of tobacco should therefore be avoided Psychotherapy and even simple reassurance concerning the nature of the condition may reduce its severity by allaying excessive fear If the basal metabolic rate is low thyroid substance should be tried Vaso dilator drugs (see p 1178) taken immedi ately before the extremities are exposed to *cold will abort some mild attacks* Repeated reactive hyperemia and contrast baths have been used At best however medical meas ures provide only partial relief

Vasoconstrictor tone is an important fac tor in bringing on and maintaining attacks of vasospasm whether or not the local ar teries are abnormally reactive to cold Re moval of vasoconstrictor impulses by re *gional sympathectomy is the treatment of* choice for the progressive type of Raynaud s disease with increasing distress indolent ulcers local gangrene or early diminution of vasodilator response in the digits If trophic changes or complications are well advanced the usefulness of the operation will depend upon the degree to which the normal capacity for vasodilatation is pre *served as shown by the vasodilator response*

In early Raynaud s disease of the lower extremities lumbar sympathetic ganglion ectomy which is essentially a preganglionic sympathectomy gives complete relief of symptoms For the upper extremity cervico dorsal ganglionectomy being a postgang lionic sympathectomy is much less efficient because of technical difficulties and frequent return of vasospasm through sensitization of the peripheral vessels probably to circulat ing epinephrine The more recently devised preganglionic cervicodorsal sympathectomy apparently avoids sensitization and postop erative vasospasm *and produces greater re* lief of symptoms (Smithwick Telford)

After successful sympathectomy sweating is absent in those areas of skin which have been *deprived of sympathetic impulses* Cer vicodorsal ganglionectomy produces Hor ner's syndrome but preganglionic cervico dorsal sympathectomy does not After opera tion if sensitization of the denervated vessels is avoided the extremities will be warmer to a degree, which can be gauged roughly by preoperative vasodilatation tests In late Raynaud s disease when the digital vessels *are hypersensitive to cold, exposure* may still produce color changes after sympath ectomy of either type but the attacks are less severe and in general, less persistent In patients with complications such as scleroderma or arthritis vasospasm may be relieved with or without improvement of the associated disease

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SCLERODERMA

(Scleroderma Sclerema Adultorum Dermatosclerosis)

Scleroderma is a localized or diffuse fibrotic contraction and atrophy of the skin and subcutaneous tissues sometimes asso ciated with paroxysmal digital cyanosis of the Raynaud type

Etiology and Incidence—The specific etiology of generalized scleroderma is un known The symmetrical form which in

volves the digits in Raynaud s disease (*sclerodactyly*) *appears to be secondary to* repeated severe ischemia Vasomotor abnormality fails however to explain the more widespread form of scleroderma which involves the subcutaneous tissues and even the underlying muscle

Scleroderma occurs most frequently in the middle period of life, females are more frequently affected than males

Pathology —Proliferation of preexisting bundles of connective tissue is accompanied by perivascular and periglandular infiltration with lymphoid cells The smaller arteries show changes similar to those observed in Raynaud s disease but in addition the minute vessels are compressed by overgrowth of fibrous tissues and the epidermal structures are atrophied

Symptoms and Signs —The cutaneous changes pass through successive stages of brawny *edema induration or hardening* atrophy and finally deformity with ulceration Atrophy may be restricted to a few punctate areas (morphea) or may involve a whole limb, large areas coalescing until finally the entire body is encased in a rigid shell The disease may appear acutely within a few days or weeks but more usually begins insidiously and requires years for full development Remissions even spontaneous disappearance have been observed Digital pallor or cyanosis of the Raynaud type on exposure to cold may precede the cutaneous atrophy *by years (usual in sclerodactyly)* or may appear only late in the stage of induration Difficulty in making accustomed movements is an early complaint Pain is often absent throughout but paresthesias numbness tingling or burning pain may appear in the prodromal stage The skin is finally either pearly white or pigmented and atrophy is accompanied by anhidrosis coldness of the digits loss of hair and the development of indolent painful ulcers The digits are tapered (acromicria) the nails curved and irregular Cutaneous induration impairs mobility of the peripheral joints and the muscles become flabby and lose their fusiform contour owing to disuse or sclerosis Atrophy of the facial skin produces a typical mask and mastication becomes difficult The bones often show rarefaction especially in the distal parts of the extremities In the early stages of scleroderma the vasodilator *response in the digits remains normal* but later is conspicuously reduced because of slight organic arterial occlusion combined with compression by fibrosis

Fever is usually absent but subacute febrile periods with diffuse pain, digestive disturbances and general malaise occur in some cases The blood reveals nothing distinctive

Diagnosis —For practical purposes scleroderma may be divided into two types The vascular form follows Raynaud s disease and involves especially exposed areas such as the hands forearms face neck and scalp The so called amorphous type bears at first little relation to vasospastic phenomena or exposure to cold If vasospasm occurs it is secondary and appears late in the course of the disease

Prognosis —Sclerodactyly occurring in Raynaud s *disease is progressive unless* vasospasm is abolished or made less severe Scleroderma of the slowly advancing generalized type passes through many periods of activity and remission during which extension to a new area may be accompanied by remission in areas earlier involved Disability may finally be extreme and then difficult respiration and mastication predispose patients to incidental infection which is the usual cause of death

Treatment —Local heat massage hydrotherapy and softening ointments containing *pilocarpine (1 per cent) or salicylic acid* (1–2 per cent) are beneficial The oral administration of salicylates and thyroid substance has been recommended frequently

In the vascular form with conspicuous vasospasm and a normal vasodilator response protection from cold vasodilator drugs and sympathetic ganglionectomy can be recommended according to the principles and limitations described under treatment of Raynaud s disease Acetyl β methylcholine by iontophoresis is said to cause regression of lesions but in many patients relapse follows The administration of ammonium chloride has also been used with occasional success partial parathyroidectomy has been recommended but the results have been uncertain

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ERYTHROMELALGIA

Erythromelalgia (Weir Mitchell 1872) is a primary or idiopathic form of paroxysmal bilateral vasodilatation associated with burning pain increased skin temperature and more or less redness of the skin

Etiology and Incidence—The etiology is unknown nor has any uniform pathology been found thus far The characteristic localized and symmetric vasodilatation has been ascribed tentatively to hyperactivity of the vasomotor (dilator) mechanism in the spinal cord Erythromelalgia occurs rarely its incidence at the Mayo Clinic being 1 in 40 000 general patients and 0 5 per cent of patients with peripheral vascular conditions The disease occurs with equal frequency in men and women without special age incidence The lower extremities are more commonly affected

Symptoms and Signs—The onset is gradual and symptoms may remain mild for years or may become so severe and continuous that total disability results Attacks of bilateral burning pain superficial or deep first involve circumscribed areas on the soles or palms but later may spread over the whole extremity The attacks follow stimuli which normally induce only physiologic peripheral vasodilatation or engorgement, *viz* local heat a warm environment exercise standing or simple dependency of the extremity In the affected areas skin temperature rises abruptly to between 33° and 37° C exceeding the temperature observed normally with maximal vasodilatation Local redness of the skin may or may not be striking depending upon the degree to which the minute vessels share in the arteriolar dilatation Arterial pulsation is increased locally and the affected skin often sweats profusely but trophic changes gangrene and ulceration are absent Rest elevation of the extremity and local application of cold relieve the congestion, hyperthermia and pain

Diagnosis—The essential criteria are (1) attacks of bilateral localized burning pain in the extremities, (2) conspicuously elevated skin temperature with more or less redness in the affected area during the attack (3) initiation and aggravation of pain by dependency heat and exercise (4) relief of pain by elevation cold or rest and (5) absence of other conditions which produce peripheral pain and redness secondarily

Polycythemia vera and arteriosclerosis produce localized burning pain which is often unilateral and accompanied by redness but little or no change in skin temperature Many chronic inflammatory states produce in the skin a susceptible state (Lewis) with diminished capillary and arteriolar tone Burning pain (erythralgia, Lewis) is then induced by mild grades of heat cold friction and congestion which leave normal skin unaffected Neuritis infectious ganglionitis and poisoning by thallium lead or arsenic occasionally produce painful peripheral hyperemia

Exposure to cold stimulates vasoconstriction which if unduly prolonged normally gives way to a temporary reactive vasodilatation of the cutaneous vessels in response to a histamine like substance liberated by local tissue damage (Lewis) In susceptible individuals an exaggerated and prolonged reactive vasodilatation after exposure to cold produces chilblains which are local areas of persisting hyperemia redness and low grade edema with tingling and pain In more susceptible patients cold produces pronounced edema of the angioneurotic or urticarial type with increased skin temperature which persists for twelve to twenty four hours A still more exaggerated local vasodilatation after exposure to cold is accompanied by systemic effects similar to those produced by injecting histamine intravenously *viz* flushing of the face tachycardia decreased blood pressure faintness and syncope

Glomus tumor and arteriovenous fistula produce venous engorgement local pulsation and increased skin temperature but not the type of pain observed in erythromelalgia

Treatment —The therapy of true erythromelalgia is in general unsatisfactory Attacks can be avoided or aborted by rest elevation of the extremity and cold applications Contrast baths using heat below the threshold for pain and local irradiation often afford considerable relief at least temporarily Very severe attacks require liberal doses of sedative Acetylsalicylic acid (0.3–0.6 Gm) relieves pain in some cases Occasionally section or alcohol injection of peripheral nerves is required, sympathectomy has been advocated

E M LANDIS

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THROMBO ANGIITIS OBLITERANS

(*Presenile Gangrene Buerger's Disease*)

Thrombo angiitis obliterans is an inflammatory type of obliterative vascular disease affecting chiefly the peripheral arteries and veins especially of males during early adult life Identified first as endarteritis obliterans (von Winiwarter 1879) it was described more fully and given its present name by Buerger (1908)

Etiology —Specific etiology is unknown although infection or the activity of some toxic agent is generally taken to be responsible Bacteria have been isolated from lesions and a type of angiitis has been induced occasionally by transplantation of diseased vessels Systemic reactions characteristic of infection are lacking and infection alone does not explain the sex incidence of the disease Recent work indicates that most patients with thrombo angiitis obliterans also have acute or chronic epidermophytosis and are sensitive to extracts of certain fungi Present evidence does not indicate whether this association is of etiologic importance or merely the result of the general vulnerability of ischemic tissues to infection

Cigarettes are used moderately or excessively by many but not all patients with thrombo angiitis obliterans Smoking produces transient vasoconstriction and probably favors extension of the disease but evidence that tobacco is the primary etiologic factor is lacking Allergic responses to tobacco can be identified in some patients but not in others The disease occurs occasionally *in persons who have never used* tobacco in any form

Constitutional or racial predisposition seems less important than formerly because in recent years authentic cases have been reported in many countries and in practically all races Occurrence in several members of a family and in identical twins has been described Chronic ergotism and abnormalities of calcium or choline metabolism have been mentioned as possible etiologic factors Exposure to cold and repeated trauma favor reactivation and extension of the disease but are not primary causes

Incidence —All races are subject to thrombo angiitis obliterans but approximately half the patients are Jews The average incidence is 1 case in 500 general admissions and approximately 50 per cent of peripheral vascular cases Males are affected far more frequently than females in a ratio of seventy five to one In females the disease is mild and may often escape diagnosis Thrombo angiitis obliterans has been observed at all ages from seventeen to seventy three but occurs most frequently between twenty and forty five

Pathology.—The lesions are segmental in that diseased sections of arteries or veins are separated by areas which are still normal In the acute stage cellular proliferation of the intima is accompanied by the formation of red thrombi Giant cells are found occasionally Polymorphonuclear leukocytes and lymphocytes infiltrate all coats of the artery and extend into the thrombus which is gradually organized Finally the occluded artery

the venae comites and contiguous nerves are bound inseparably into a bundle of hard fibrous cords New segments of artery or vein are involved acutely at intervals varying from days to years, hence a single long artery commonly exhibits many stages of the cycle ranging from earliest intimal proliferation to dense scar formation Many partly organized thrombi are recanalized thus aiding the conspicuously enlarged collateral vessels in restoring peripheral circulation

Symptoms and Signs—Thrombo angiitis obliterans follows a relapsing course in that periods of extending arterial involvement alternate with periods of quiescence during which developing collateral circulation gradually assumes, more or less efficiently the function of the occluded vessels Depending upon the relation between those two concurrent processes of occlusion and compensation the onset varies from insidious to fulminant Ordinarily occlusion gradually outstrips the developing collateral circulation and definite peripheral ischemia brings the patient to the physician within one to four years after the first mild symptoms appear In fulminating or acute cases the whole course is condensed into a few months The disease ordinarily runs an active course of six to twelve years and then advances much less rapidly

The most frequent initial symptom is persistent coldness of one or both lower extremities and less commonly of the upper extremities Aching pain in the digits instep ankle calf (intermittent claudication) wrists or forearm follows exercise of the corresponding muscles Migratory phlebitis may precede or accompany arterial involvement and occasionally the veins alone are affected Tender red elevated areas about 1 cm in diameter appear suddenly in the skin near the valves of the small superficial veins of the foot or lower leg and gradually disappear during two or three weeks to be followed after irregular intervals by new lesions The patient may have observed cutaneous color changes such as cyanosis rubor or even cyclic digital cyanosis and redness of the Raynaud type Trivial trauma ill-advised minor surgery excessive heat or irritant local medication may produce a small ulcer which instead of healing rapidly extends and becomes painful This type of "rest pain" is continuous and is usually worse at night in contrast to the pain of intermittent claudication which is produced by activity and relieved by rest Agonizing pain sleeplessness and excessive smoking frequently form a vicious cycle as the ulcer extends and gangrene develops Rest pain arising from thrombosis and ulceration is generally burning gnawing or aching in type and tends to be constant while the rest pain of ischemic neuritis, which may occur without cutaneous lesions, is paroxysmal and often lancinating Gangrene is usually moist from the beginning but local resistance to extending infection is much higher than in arteriosclerotic or diabetic gangrene

Examination reveals coldness of the involved extremity with reduced or absent arterial pulsation Elevation of the extremity produces pallor and dependency produces cyanosis The grade of rubor trophic changes and wasting of muscles depends upon the duration and severity of peripheral ischemia Vasodilatation tests reveal definite organic vascular occlusion with coexisting vasospasm in one or more extremities When the patient is first seen the disease is usually well advanced in one extremity while the opposite one presents at least vasospasm and frequently mild organic occlusion Although the lower extremities are most frequently involved the disease begins occasionally in the small arteries of the hands Moreover, thrombosis of the mesenteric coronary cerebral or renal arteries is not uncommon

Roentgenograms usually reveal osteoporosis and occasionally osteomyelitis of the phalanges In elderly patients roentgenographic or clinical evidence of arterial calcification does not exclude thrombo angiitis obliterans which may occur in association with arteriosclerosis

Diagnosis—Typical thrombo angiitis obliterans when fully developed in the lower extremities of a young male can hardly be confused with other conditions Paroxysmal cyanosis of the digits sometimes leads to an erroneous diagnosis of Raynaud s disease which in contrast to thrombo angiitis obliterans is rare in males affects the upper extremities more severely and does not obliterate arterial pulsation at the wrist and ankle Thrombophlebitis is accompanied by

normal arterial blood flow and a normal vasodilator response In the elderly with arteriosclerosis the certain diagnosis of thrombo angiitis may require histologic study of an excised vein unless classic migratory phlebitis has been observed

Failure to recognize early stages of thrombo angiitis obliterans is the common error Patients frequently wear a succession of orthopedic appliances for fallen arches before it is recognized that the pain in the ankle or instep is due to organic vascular disease Gangrene may be precipitated by excessive heat (baking) strong antiseptics or ill advised avulsion of a nail for pain or persisting paronychia The rubor of long standing ischemia will not be mistaken for inflammatory reaction if the coldness of the foot and the absence of arterial pulsation are observed

Treatment—Early diagnosis is an important prerequisite for instituting preventive measures to avoid the more serious complications and eventual disability Warm clothing should be worn routinely with fleece-lined gloves or shoes Patients should avoid exposure to cold and if possible obtain sedentary indoor occupation The potential *dangers of trauma minor surgery and dermatophytosis* should be explained The skin should be kept scrupulously clean dry and soft, with frequent inunctions of a bland oil Tobacco should not be used in any form In mild cases without lesions contrast baths postural exercises (Buerger Allen) diathermy and warm sitz baths will increase peripheral blood flow at least temporarily Reflex vasodilatation of those vessels still capable of expanding may be produced by applying electric heating pads to two of the unaffected extremities for a period of forty five minutes several times weekly Foci of infection should be eradicated to avoid possible reactivation of the disease during pe*riods of reduced resistance*

A large fluid intake 3 to 4 liters per day with 5 to 10 Gm of sodium chloride induces hydremia and may relieve distressing nocturnal cramps Intravenous injections of sodium citrate hypertonic sodium chloride solutions or sodium thiosulfate in repeated courses have been recommended Insulin free extracts of pancreas injected intramuscularly diminish the severity of intermittent claudication apparently by aiding metabolism of muscle but do not affect ulcers or rest pain If basal metabolism is low, thyroid substance or thyroxin may be of value The administration of calcium has been recommended

If rest pain is present, with or without lesions absolute rest in bed is essential The affected extremities should be kept horizontal or 20 to 30 degrees below horizontal The latter position aids peripheral blood flow and occasionally is the only one that the patient can tolerate The development of edema and pressure areas should be guarded against External warmth is best applied by means of a thermo regulated cradle kept at the temperature at which the patient is most comfortable usually between 30° and 34° C (Starr) Infected lesions should be kept open moist and clean by means of warm boric acid compresses Antiseptics must be used with caution because of the danger of injuring tissues already partially devitalized Ointments containing sulfonamide drugs are helpful but maceration must be avoided

Typhoid vaccine is given intravenously in ascending doses every four to seven days in spaced courses of eight to sixteen injec*tions The smaller doses do not produce* a chill but may still be followed by vasodilatation relief of pain and healing of ulcers The usefulness of vasodilator drugs (see p 1178) is limited by the degree of organic occlusion but they should be tried because of the conspicuous relief occasionally obtained Suction and pressure therapy intermittent venous occlusion or the oscillating bed may be used cautiously to increase blood flow temporarily in crises of ulceration and rest pain but are useless with massive gangrene or osteomyelitis Spreading infection or recent phlebitis contraindicate their use

Rest pain may also be relieved by anal*gesic ointments applied directly* to lesions and by the oral administration of acetyl salicylic acid acetanilid phenobarbital codeine or morphine with *precautions against* addiction The alcoholic injection or crushing of peripheral nerves produces anesthesia which persists for two to six months when the operation may, if necessary be repeated Chordotomy though occasionally used is rarely if ever indicated

Bilateral sympathetic ganglionectomy has been advocated for the treatment of established gradually advancing thrombo angiitis obliterans with symptoms dating back two years or more, if organic occlusion is not pronounced and if vasospasm is prominent This major operation is not indicated in mild cases responding well to medical treatment nor in advanced cases with massive gangrene and gross organic vascular occlusion The operation is said to have a certain prophylactic value in that the opposite extremity is involved less frequently and less severely Opinion is still divided concerning the general usefulness of sympathetic ganglionectomy in the treatment of thrombo angiitis obliterans The mortality of the operation is extremely low in most conditions but in thrombo angiitis obliterans amounts to 6 per cent primarily on account of lesions in more centrally placed vessels

In skilled hands paravertebral *injection of alcohol* is an effective method of blocking sympathetic impulses and releasing vasospasm Periarterial sympathectomy is at best a temporary expedient Arteriectomy and venous ligation have been abandoned in most clinics

In thrombo angiitis obliterans resistance to systemic infection is fairly high and collateral circulation is usually good so that minor amputations may be performed more safely than is the case in arteriosclerotic gangrene In the presence of ascending infection advancing lymphangitis fever and leukocytosis the oral administration of *sulfonamide* drugs is indicated but delaying amputation is hazardous because the efficacy of the sulfonamides is markedly limited by ischemia of the affected tissues and by local necrosis The oscillometer reactive hyperemia and the histamine test will assist in deciding the safe level for amputation High amputations are required in elderly patients and in those with progressive gangrene rapidly ascending infection or extensive destruction of tissue

E M LANDIS

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ERGOTISM

Ergotism is an acute or chronic intoxication arising from the ingestion of bread made from rye or wheat infested with ergot fungus (*Claviceps purpurae*) Diarrhea colic and vomiting are followed by headache vertigo, paresthesias convulsive seizures and occasionally gangrene of the digits nose or ears It occurred during the past in epidemic form but it is now seen only sporadically, or after the repeated administration of ergot in abortion and of ergotamine in pruritus Peripheral gangrene is due to long continued arteriolar spasm and slow blood flow with secondary intimal hyperplasia and thrombosis In chronic intoxications the convulsive form is said to affect especially women children and the aged while the gangrenous form is more frequent in males during early adult life

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PERIARTERITIS NODOSA

Periarteritis nodosa (Kussmaul and Meier 1866) is a form of inflammatory panarteritis affecting any of the medium sized and small arteries and accompanied by systemic symptoms of infection with added regional symptoms depending on the organs involved

Etiology and Incidence—The specific etiologic agent is unknown among the causes suggested are the streptococcus a filtrable virus or bacterial hyperergy The occurrence of this condition in patients who have suffered from asthma serum sickness or sulfonamide reactions argues strongly in favor of an anaphylactic type of hypersensitivity This view is further supported by the experimental production of characteristic lesions in rabbits by the repeated injection of horse serum (Rich) The disease also occurs occasionally in association with rheumatic endocarditis scarlet fever and tonsillitis Periarteritis nodosa is relatively rare approximately 200 cases having been so far described Both sexes are affected at all ages approximately 50 per cent of cases occurring in the third and fourth decades

Pathology—The adventitia the vasa vasorum and the loose perivascular tissues are infiltrated by polymorphonuclear leukocytes lymphocytes and often eosinophils In addition necrosis of the media and the elastic fibers leads to the formation of multiple small arterial aneurysms which may be followed either by fibrosis or eventual rupture with hemorrhage and ecchymosis Intimal proliferation and degeneration lead to thrombosis and arterial obstruction Repair and fibrosis of the adventitial lesions produce characteristic nodules which can be felt along the course of the artery Ischemia mild or severe may occur in any organ through involvement of the corresponding artery Veins are affected more rarely and less conspicuously

Symptoms and Signs—The onset varies from insidious to violent with moderate fever sweating tachycardia malaise fleeting edema and progressive weakness accompanying diffuse joint, muscular or abdominal pain Secondary anemia develops sooner or later with moderate or severe leukocytosis and occasionally conspicuous eosinophilia The liver and spleen may be palpable and the muscles are usually atrophied and tender Blood pressure may be slightly elevated In contrast to thromboangiitis obliterans the visceral arteries are more frequently affected than are the peripheral arteries and local symptomatology is therefore extremely variable Severe internal hemorrhages may occur Renal involvement *is common the urinary signs resembling* those of acute glomerulonephritis The clinical picture may however be that of gastro intestinal hepatic cardiac or organic nervous disease Cutaneous hemorrhages urticaria purpura and tender reddened subcutaneous nodules appear in the extremities Peripheral thrombosis leads to arterial occlusion and digital gangrene The prognosis is poor and although remissions occur recovery has been rare in the cases so far reported

Diagnosis formerly depended almost exclusively upon the discovery of typical pathologic changes in arteries removed at autopsy The examination of biopsy material has led to more frequent diagnosis during life

Treatment is chiefly supportive including repeated blood transfusions and symptomatic therapy for associated conditions Irradiation and neoarsphenamine have been used with occasional success In view of recent work every effort should be made to exclude antigens that might be responsible

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SYSTEMIC INFECTIONS PERIPHERAL ARTERITIS AND GANGRENE

Symptoms and signs of peripheral vascular disease mild or severe appear occasionally as complications in typhoid fever typhus pneumonia, influenza cholera bacterial endocarditis septicemia and scarlet fever Mild focal degeneration of the media of the large arteries occurs frequently without producing vascular symptoms Outspoken necrosis of the media and intimal hyperplasia may lead to thrombosis with signs of subacute or acute arrest of peripheral blood flow Peripheral ischemia may be transitory and in large part, vasospastic On the other hand thrombotic vascular occlusion affecting small arteries produces necrosis of the skin while occlusion of large arteries leads to massive gangrene

Tuberculosis of the peripheral arteries is rare but occasionally metastatic infections or embolism produce panarteritis or endarteritis with fully developed tubercles in thrombosed vessels Direct involvement by extension from adjacent tuberculous lesions while common in centrally placed vessels is very rare in the extremities

Syphilis may diminish peripheral circulation by producing periarteritis obliterative intimal hyperplasia or panarteritis but the media is much less affected than is the case in the large elastic arteries True gummata have been found in the vessels of gangrenous limbs Peripheral vascular complications of syphilis are more common in males than in females Peripheral ischemia vasospastic or organic appears insidiously or suddenly but gangrene is rare Active antisyphilitic therapy ordinarily arrests the acute progress of the disease and relieves early vasospasm but organic occlusion remains

E M LANDIS

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PERIPHERAL ARTERIOSCLEROSIS

(Senile Gangrene Diabetic Gangrene Thrombo arteriosclerosis Obliterans Monckeberg s Sclerosis)

The etiology pathology and general symptomatology of arteriosclerosis are discussed on pages 1160–1166 Only peripheral manifestations and their treatment need be considered in this section

Incidence —Peripheral vascular symptoms of arteriosclerotic origin are common in the lower extremities rare in the upper extremities They occur more frequently in men than in women and are more apt to be unilateral than is the case in thrombo angiitis obliterans Symptoms arise with increasing frequency after fifty years of age the average age of hospital patients with fully developed arteriosclerotic peripheral vascular disease being about sixty Diabetes lowers the average age incidence of developed peripheral arteriosclerosis by ten years and if severe and uncontrolled may produce vascular symptoms at any age

Symptoms and Signs.—In most instances peripheral ischemia has begun insidiously long before symptoms appear Coldness of the extremities paresthesias dysesthesia or painful nocturnal cramps may precede intermittent claudication and obvious peripheral cyanosis or rubor Intermittent claudication may be present though digital circulation is good On the other hand mild cardiac failure or angina pectoris may restrict activity so that intermittent claudication is never a prominent feature in spite of advanced occlusion Many elderly persons with marked arterial occlusion and a very narrow margin of safety remain relatively free from symptoms for long periods until trauma or local infection precipitates indolent ulceration and violent rest pain In others without obvious cause sudden thrombosis produces slaty cyanosis of one or more digits with rest pain often of the neuritic type Both pain and cyanosis may gradually disappear as collateral circulation develops but more commonly the affected skin becomes wrinkled and the involved tissues mummify with slow demarcation or become ulcerated as infection occurs

Examination usually reveals obvious vascular sclerosis in the extremities and else-

where The feet are cold pale when elevated and cyanotic when dependent Cyclic color changes of the Raynaud type are occasionally observed in the digits Arterial pulses cannot be felt in the affected extremity and the arteries are sometimes palpable as irregular cords The skin is dry scaly and atrophic the muscles flabby and the nails brittle beaked or ridged Ulcers are indolent with pale, edematous granulations and cyanotic borders The vasodilator response is diminished or absent but vasospasm is not a conspicuous feature Roentgenographic study usually reveals calcification of the peripheral arteries The degree of calcification bears no relation to the grade of peripheral ischemia since calcium deposition is often confined to the media as in Monckeberg s sclerosis

In patients with diabetes arterial obliteration is occasionally limited to segments of small arteries while the larger vessels are still only moderately diseased Local trauma produces superficial cutaneous gangrene although the posterior tibial and dorsalis pedis arteries pulsate normally and the foot in general is warm This type of gangrene due to blockage of arterioles and small arteries responds well to conservative therapy On the other hand diabetic patients with advanced occlusive disease of the large arteries are especially apt to develop lymphangitis and *systemic infection from trifling lesions* because their resistance to infection is extremely low Rest pain is usually less severe in diabetic patients than in those with simple arteriosclerosis

The prognosis of arteriosclerotic peripheral vascular disease simple or diabetic is at best grave because infection is apt to spread rapidly and collateral circulation develops very slowly except in young patients with well controlled diabetes Prognosis must be guarded also because thrombosis is particularly apt to involve the origin of the posterior and anterior tibial arteries a location in which collateral blood supply is especially precarious

Diagnosis—When thrombo angiitis obliterans occurs in the elderly it is usually of the chronic type and resembles arteriosclerotic peripheral vascular disease in its course and therapeutic limitations Ischemia of the spinal cord secondary to sclerosis of the spinal arteries produces intermittent weakness and spasticity of the leg muscles with early fatigue and weakness but not the true pain of intermittent claudication

Treatment—Cardiac insufficiency especially when due to disorders of rhythm may exaggerate peripheral vascular symptoms for this reason appropriate general treatment is indicated when peripheral vascular symptoms are associated with cardiac disease Prompt diagnosis of *early peripheral* arteriosclerosis permits prophylactic care and avoids the more serious complications while careful control of diabetes diminishes the rate at which arteriosclerosis develops Detailed instructions concerning protection against general or local chilling should be provided The potential dangers of trivial trauma or mild infection cannot be overemphasized The skin must be kept scrupulously clean dry and soft a bland oil being used if necessary The use of tobacco though perhaps not so deleterious as in thrombo angiitis obliterans should be prohibited Contrast baths postural exercises diathermy and warm sitz baths may be used cautiously

A generous fluid intake with 5 to 10 Gm of sodium chloride daily will occasionall relieve distressing nocturnal cramps but must be discontinued if edema develops The intravenous injection of hypertonic solution *of sodium chloride has been recommended* Intramuscular injections of insulin free extracts of pancreas apparently aid muscle metabolism and will often decrease the severity of claudication though they do not help rest pain or indolent lesions

For rest pain with or without ulcers absolute rest in bed is essential The affected extremity should be kept in the optimal position usually horizontal or 20 to 30 degrees below horizontal with precautions against the development of edema and pressure areas External heat is best applied by means of the thermo regulated cradle set at 30° to 34° C (Starr) Calcium chloride trays in the cradle are *helpful in preventing moist* gangrene If moist dressings are required bland solutions *e g* boric acid compresses are safer than stronger antiseptics Sulfonamide ointments can be used with benefit if maceration of the skin is guarded against The intravenous administration of typhoid

vaccine is contraindicated because during the chill thrombi are apt to form in sclerotic vessels The usefulness of vasodilator drugs (see p 1178) depends upon the grade of organic occlusion Beverages containing ethyl alcohol in doses up to 0 5 cc per kilo at four- to five hour intervals, have both analgesic and vasodilator action Reflex vasodilatation may be produced by encircling the forearms in electric heating pads for forty five minutes several times weekly Suction and pressure therapy intermittent venous occlusion or the oscillating bed may be useful in conjunction with other procedures, particularly for the pain produced by ischemic neuritis or indolent lesions Suction and pressure therapy is given in one hour periods at first several times daily gradually diminishing to three hours per week as symptoms recede Intermittent venous occlusion and the oscillating bed can be used for much longer periods or even continuously if edema does not develop These physical measures are all contraindicated in the presence of spreading infection or recent phlebitis and must be used with great caution in treating extremities with open lesions

For rest pain due to lesions analgesic ointments may be applied locally Acetylsalicylic acid, acetanilid phenobarbital codeine or morphine are usually required in addition Crushing of peripheral nerves relieves pain effectively but is sometimes followed by sloughing wounds because of widespread organic occlusion

Sympathetic ganglionectomy is generally contraindicated because vasospasm is not prominent and because the age and clinical state of the patient often exclude a major operation Periarterial sympathectomy a minor procedure produces at best temporary results but is occasionally worthy of trial in the elderly Ligation of veins and arteriectomy have been recommended but are not generally accepted as routine procedures

In the presence of ascending infection advancing lymphangitis fever and leukocytosis the oral administration of sulfonamide drugs is indicated but delaying amputation is hazardous because the efficacy of the sulfonamides is markedly limited by ischemia of the affected tissues and by local necrosis In contrast to the safety of minor surgery in thrombo angitis obliterans amputation of digits for local gangrene due to peripheral arteriosclerosis is successful in *only 10 per cent of cases* and if diabetes is present, healing occurs in only 5 per cent. Minor amputations may however be attempted for osteomyelitis of terminal phalanges without gangrene and for sharply localized gangrene at the tip of the digits when pulsations can be felt clearly in the dorsalis pedis and posterior tibial arteries High amputation is required for spreading infection extending gangrene or intractable rest pain with widespread occlusion

E M LANDIS

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(see also *Thrombo angitis Obliterans*)

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EMBOLISM

Dislodged fragments of centrally located thrombi may produce sudden occlusion of the peripheral arteries Emboli usually originate from mural or valvular thrombi in the left side of the heart and less commonly from an atheromatous ulcer in a large artery Predisposing factors include (1) change from auricular fibrillation to normal rhythm (2) bacterial endocarditis and (3) coronary occlusion with mural thrombosis Large emboli lodge most commonly at branchings of the larger arteries *viz* at the origin of the iliac arteries (saddle or rider embolus) at the junction of the femoral artery with the profunda femoris and at the junction of the subscapular and axillary arteries The embolus (1) stops blood flow through the vessel in which it lodges (2) induces widespread secondary vasospasm in

the affected extremity and (3) is followed within a few hours by secondary thrombosis below and sometimes above the point of obstruction

Symptoms and Signs —Onset is usually sudden with severe pain in the region where the embolus lodges, the sensation may resemble that of a blow on the extremity When large arteries are occluded fainting nausea vomiting abdominal pain and local tenderness may precede a shock like state The extremity is pallid and cold while paresthesias such as numbness or tingling develop rapidly Within one or two hours pain in the extremity is often agonizing sensation is absent and muscular weakness or paralysis has developed The initial pallor changes to blotchy cyanosis and if treatment is delayed massive gangrene follows with mummification, bleb formation and spotty vermilion discoloration of the skin Very small emboli produce local cyanosis with or without pain

On examination the extent of coldness and discoloration indicates roughly the size of the vessel affected but it must be remembered that ischemia from secondary vasospasm is added to that from embolic obstruction *per se* Arterial pulsation cannot be detected by finger or oscillometer distal to the embolus Anesthesia paralysis and absence of reflexes are found if large arteries are occluded The oscillometer histamine wheals and skin temperatures will indicate the boundary between normal and abnormal blood flow

Treatment —Early diagnosis is essential since the operation of embolectomy to be successful must be done within eight or ten hours after the embolus has lodged Embolectomy is less often necessary in the upper extremity where collateral circulation is good If the patient is seen early it is best to abolish the widespread reflex vasospasm before deciding definitely whether embolectomy is advisable or not The immediate results of operation are good but new emboli may appear and the mortality after operation is usually due to the underlying condition

In all cases vasoconstrictor tone should be relieved as soon as possible (1) by the paravertebral injection of procaine to block the sympathetic ganglia (2) by administering alcohol by mouth or papaverine hydrochloride intravenously and (3) by warming the body and the uninvolved extremities The affected limb should be placed in a thermo regulated cradle to prevent the burning and trauma which follow the indiscriminate use of uncontrolled heat Heparin is given intravenously to prevent secondary thrombosis The oral administration of dicoumarin for prolonged anticoagulant activity is still in the experimental stage Suction and pressure therapy, applied early and carefully at frequent intervals, is a useful adjuvant measure

The advisability of amputation will depend upon the degree to which collateral circulation fails to compensate for sudden organic occlusion the general condition of the patient and the underlying condition responsible for embolism

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FROST BITE

Frost bite results from exposure to cold combined with prolonged physiologic peripheral vasoconstriction Simple exposure of the digits to cold produces local vasoconstriction which if the body is warm gives way periodically to protective reactive hyperemia If body temperature is reduced however physiologic increase in vasoconstrictor tone prevents further loss of body heat and at the same time abolishes this protective local reaction Maintaining body temperature is more vital to the organism than preserving digital tissue

Frost bite appears after prolonged exposure to wind and moist cold usually but not necessarily below 8° F General weakness and peripheral vascular disturbances are predisposing factors The local injury produced by cold ranges from simple erythema transient anesthesia and superficial bullae to persisting ischemia secondary thrombosis livid cyanosis and gangrene

Prophylactic measures include the wearing of warm dry clothing, only brief periods of exposure to cold with avoidance of smoking before and during exposure After local injury has developed the patient should be made warm as quickly as possible The affected parts may be massaged very gently for a few minutes only and then wrapped in sterile dressings and several layers of wool Too vigorous warming and reactive hyperemia may produce severe pain which can be alleviated by immersing the extremity for brief periods in water at 10° to 15° C If on the other hand vasodilatation is slow and incomplete vasodilator drugs (alcohol papaverine or others) and a thermoregulated cradle set at not more than 34° C will be helpful Direct heat especially if uncontrolled, and diathermy are to be avoided because excessive warmth produces pain with marked edema and greater tissue destruction

Suction and pressure therapy in brief repeated periods is helpful for prolonged ischemia Sepsis and gangrene may require amputation at levels depending upon the line of demarcation and the amount of secondary thrombosis

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GLOMANGIOMA OR GLOMUS TUMOR

(*Painful Subcutaneous Nodule Angioneuroma or Angiomyoneuroma*)

Glomangioma or glomus tumor designates painful, benign hypertrophy of an arteriovenous anastomosis with its associated smooth muscle coat nonmyelinated nerve fibers and connective tissue (collectively termed a glomus) Histologically the lesion is encapsulated occasionally diffuse but never invasive and contains numerous glomus' cells without inflammatory reaction These extremely tender but inconspicuous subcutaneous tumors develop very slowly during adult life often following slight trauma They are found in various parts of the upper and lower extremities but most frequently (30 per cent) beneath the fingernail The diameter of the tumor is 1 cm or less The intact skin or nail over the lesion is flat or slightly raised with discoloration ranging from red to blue usually the latter Excruciating burning or shooting pain both local and referred up the extremity occurs spontaneously or is produced by pressure on the tumor Heat excessive cold and even contact with clothing become intolerable so that protection is required continuously day and night The tumor may pulsate slightly and skin temperature may be elevated locally

In treatment, radium has proved useless Surgical excision brings complete and immediate relief without recurrence

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ARTERIOVENOUS FISTULA

Arteriovenous fistula refers to abnormal communications, single or multiple between arteries and veins by which arterial blood enters the vein directly without traversing a capillary network These fistulae are classified as (1) congenital usually multiple and present from birth and (2) acquired usually single and saccular arising after bullet or stab wounds involving an artery and a contiguous vein

Arterial blood following the path of least resistance rushes directly into the vein instead of through the corresponding capillary bed The thin walled veins are distended by the pressure transmitted from the artery through the fistulous opening and eventually become prominent and cirsoid Increased blood flow makes the tissues near the fistula abnormally warm while diminished capillary flow distal to the fistula produces

peripheral coldness and trophic changes Large fistulae impose a burden on the heart the output of which must be increased above normal by an amount proportional to the size of the fistula in order to maintain an efficient general circulation The low peripheral resistance tends to decrease diastolic blood pressure and increase systolic and pulse pressures Males and females are affected equally and any portion of the body may be involved

Symptoms and Signs —Patients complain of aching pain edema disfigurement from dilated veins or hypertrophied extremities and occasionally, cardiac symptoms such as palpitation substernal pain and dyspnea on exertion

On inspection the superficial veins are prominent under spongy subcutaneous tissue and venous pulsation can be felt unless the fistula is small or deeply placed Arterial pulsation is also increased and skin temperature is often elevated Local bruit and thrill occur frequently but not uniformly The tissues near the fistula may be tender more or less edematous and either red or slightly cyanotic The circumference of the extremity is increased by edema or true hypertrophy but bony structures are hypertrophied only if the fistula has been present before epiphyseal ossification occurred Distal to the fistula decreased capillary flow leads to the formation of shallow indolent ulcers rarefaction of bone and occasionally to unilateral arthritic changes Large fistulae elevate systolic blood pressure increase pulse pressure and lead to cardiac hypertrophy and even decompensation The heart rate is abnormally rapid during rest Temporary compression of the artery leading to a large fistula diminishes the heart rate but no effect is observed if the fistula is small

The oxygen saturation of blood removed from distended veins is greater than that of blood removed from corresponding veins in the opposite extremity Deeply placed fistulae require comparisons between blood samples from deeper veins Arteriography reveals the exact location number and size of the communications

Treatment —Single fistulae can be eradicated by ligating the involved artery and vein both above and below the fistula if adequate collateral circulation is available Multiple fistulae are much less amenable to surgical treatment If the arterial supply depends upon one large anomalous artery ligation of this vessel followed by stenosing injections of the dilated veins may be effective Ulcers edema and pain are relieved by applying supporting rubber bandages Amputation is required for large inoperable fistulae producing cardiac decompensation or gross deformity

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DISEASES OF THE PERIPHERAL VEINS

The conditions affecting venous blood flow in the extremities may be divided into two categories (1) intrinsic disorders which are produced primarily by disease of the walls of the veins or by abnormality of their contained blood and (2) extrinsic disorders resulting secondarily from invasion or external pressure These various maladies are disabling in proportion to the grade of venous stasis that is produced (1) by anatomic blockage as in thrombosis and external pressure or (2) by hydrostatic forces as in varicose veins

VARICOSE VEINS

Varicose veins are caused (1) by constitutionally defective valves in association with postural strain usually of occupational type or (2) by any condition which obstructs venous blood flow and distends collateral veins over long periods of time especially pregnancy and pelvic or abdominal neoplasm The veins are distended and tortuous while chronic venous stasis produces local edema stabbing or aching pain indolent ulceration overgrowth of connective tissue and occasionally hemorrhage or ecchymosis

Prophylactic measures include the wearing of warm dry clothing only brief periods of exposure to cold with avoidance of smoking before and during exposure After local injury has developed the patient should be made warm as quickly as possible The affected parts may be massaged very gently for a few minutes only and then wrapped in sterile dressings and several layers of wool Too vigorous warming and reactive hyperemia may produce severe pain, which can be alleviated by immersing the extremity for brief periods in water at 10° to 15° C If on the other hand vasodilatation is slow and incomplete vasodilator drugs (alcohol papaverine or others) and a thermo regulated cradle set at not more than 34° C will be helpful Direct heat especially if uncontrolled, and diathermy are to be avoided because excessive warmth produces pain with marked edema and greater tissue destruction

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from pneumonia, influenza or typhoid fever It may be produced by direct extension from local suppurative foci e g mastoiditis and osteomyelitis So called "resting phlebitis" in varicose veins may be reactivated periodically by trauma exercise or minor infection elsewhere Polycythemia vera and certain forms of anemia in which the coagulability of the blood is increased are frequently complicated by venous thrombosis without trauma or infection

Symptoms and Signs —Noninflammatory venous thrombosis occurs suddenly or gradually after exertion or slight contusion Edema and cyanosis appear rapidly but pain local tenderness and systemic symptoms are absent

The onset of true thrombophlebitis is usually sudden with mild or severe symptoms depending on the size of the vein involved Pain may be absent mild and localized or severe and throbbing through the whole extremity When the pelvic veins are obstructed abdominal pain faintness nausea or vomiting may appear suddenly and persist for some hours When a peripheral and superficial vein is affected the thrombosed vessel can usually be felt beneath the skin as a tender cord Local tenderness in the calf and pain on forced dorsiflexion of the foot suggest involvement of the deeper branches of the popliteal vein. Edema and mottled cyanosis are present if collateral venous drainage is poor but these signs are absent when small veins are obstructed and the collateral channels are adequate Arterial pulsation is normal and the extremity is not persistently cold Occasionally however in sudden extensive venous thrombosis vasospasm is so conspicuous temporarily that arterial embolism may be suspected but the oscillometer will detect arterial pulsation even when it is too feeble to be palpated Elevation of the extremity does not produce abnormal pallor on the contrary cyanosis may persist during elevation General malaise anorexia fever and leukocytosis appear shortly after onset and barring extension of thrombosis gradually disappear In migrating thrombophlebitis however several widely separated veins may be involved in succession healing in one location being associated with fresh thrombosis in a totally different region

The most serious complication of thrombophlebitis is pulmonary embolism which follows dislodgment of a thrombus shortly after it has formed and before organization has fixed it firmly in the vein of origin In general the greater the local tenderness and pain in the extremity the less is the danger of embolism since thrombi usually loosen before pronounced inflammatory reaction develops Large thrombi dislodged from the femoral iliac or pelvic veins commonly produce fatal pulmonary embolism, a frequent cause of sudden death after operation or deep pelvic irradiation Smaller emboli produce pulmonary infarction pleuritis bronchopneumonia or abscess

Repeated attacks of thrombophlebitis and continued venous stasis, with more or less lymphangitis cause edema fibrosis pigmentation and trophic ulceration and the eventual deformity in untreated cases may be extreme

Treatment —Since sluggish peripheral blood flow is an important predisposing factor bedridden patients can be protected from thrombophlebitis by passive movements and exercises postoperatively by avoiding dehydration and by frequent turning Additional protection has been sought by injecting heparin intravenously or more recently by giving dicoumarin orally but so far neither has been used routinely the latter especially being still in the experimental stage

Once thrombosis has developed the objects of therapy are (a) to prevent pulmonary embolism by loosened thrombus and (b) to relieve the edema before connective tissue overgrowth in the protein rich edema fluid produces permanent brawny organization Pulmonary embolism may occur suddenly before symptoms and signs of peripheral thrombosis appear Phlebotomy and removal of the thrombus (thrombectomy) have been advocated especially for simple noninflammatory thrombosis of large veins Such surgical treatment is contraindicated if diagnosis is late and if there is local inflammatory reaction However when the distal segments of superficial veins e g the long or short saphenous or the deep veins of the calf are thrombosed proximal ligation is a minor procedure which reduces the danger of pulmonary embolism

DISEASES OF THE PERIPHERAL VEINS

Intrinsic conditions	Congenital	Hypoplasia Hemangioma Arteriovenous fistula
	Mixed	Varicose veins (incompetent valves)
	Acquired	Traumatic Arteriovenous fistula Simple thrombosis (phlebothrombosis) Inflammatory Thrombophlebitis Thrombo-angiitis obliterans
	Degenerative	Phlebosclerosis
Extrinsic conditions	Invasion	Neoplasm tuberculosis
	Pressure	Neoplasm trauma anomalies gravid uterus

The extremities are warm and the arterial pulses normal Elevation of the foot produces no blanching but empties the veins rapidly unless obstruction is present when emptying is slow and incomplete Retrograde flow of blood past incompetent valves in the long saphenous vein is demonstrated by the Trendelenburg test The leg of the recumbent patient is elevated to empty the varices and then while firm pressure with the thumb or a tourniquet closes the proximal end of the long saphenous vein, the patient quickly assumes the standing position Sudden release of the saphenous vein will make the varices prominent and turgid within a few seconds if back flow is present If pressure is maintained for a longer time in the standing position dilated communications with incompetent deep veins can be identified In advanced stages the vein responsible for brawny induration and ulceration may be invisible under the deformity it has produced but careful palpation will usually detect the dilated vein Tapping a varix with the finger may produce a transmitted impulse in the long or short saphenous vein Perthes' test is helpful in demonstrating patency of the deep veins Venography has been advocated for doubtful cases Phlebosclerosis is common in chronic cases

Therapeutic measures include bed rest with elevation of the extremity rubber bandages sponge rubber dressings the gelatin boot injection of sclerosing solutions and high ligation or excision Acetyl β methyl choline by iontophoresis excision and skin grafting have been used successfully for treating chronic ulcers resisting other therapy

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THROMBOPHLEBITIS

Thrombophlebitis is a form of venous obstruction by thrombosis which is secondary to local or distant infection and is accompanied by inflammatory reaction in the wall of the affected vein It is sometimes difficult to distinguish clinically between simple noninflammatory thrombosis (phlebothrombosis) and true (inflammatory) thrombophlebitis Pylephlebitis is described on pages 760 769

Etiology ordinarily consists of one or more of several predisposing factors viz (1) venous stasis associated with prolonged bed rest or external pressure (2) local injury of the endothelium by stretching contusion chemicals or bacteria, and (3) thrombophilia or changes in the circulating blood which favor coagulation Noninflammatory relapsing thrombosis may follow simple stretching or mild contusion over a vein True thrombophlebitis occurs during prolonged bed rest with associated infection *e g* after operations intravenous therapy, in the puerperium and during convalescence

hypoplasia of the lymphatic vessels and in its secondary form to obstruction by external pressure or repeated low grade inflammation

Primary lymphedema occurs more commonly in females Three forms are described (1) congenital lymphedema present at birth or developing shortly thereafter (2) lymphedema (praecox) appearing at or near puberty, and (3) Milroy s disease (hereditary tropho edema) or lymphedema of familial type The onset is gradual and symptomless except for the increasing size of the limb The edema pits easily at first and disappears when the limb is elevated but later owing to fibrosis pits with difficulty and is not relieved by elevation Low grade lymphangitis and cellulitis absent in the early stages often appear later and add to the original deformity

Secondary lymphedema may be noninflammatory or inflammatory The former is due to compression of main lymphatic trunks by neoplasm or scar surgical removal of lymph nodes fibrosis following irradiation or direct invasion of lymph vessels or nodes by neoplasm

Secondary lymphedema of the inflammatory type follows recurrent low grade lymphangitis In tropic and subtropic regions filariasis must be considered Each attack of lymphangitis produces additional edema which disappears only partially after acute inflammation subsides Recurrences at irregular intervals are due to reinfection from the exterior or to intermittent activity of foci in the extremity itself The edema fluid contains considerable protein and offers an excellent medium not only for recurrent bacterial invasion but also for overgrowth of connective tissue The skin finally becomes thick coarse folded and hard and the extremities are subject to indolent ulceration erysipeloid infection and excoriation so that the eventual deformity may be extreme well deserving the name elephantiasis

Treatment —Painstaking care in keeping the tissues free of edematous fluid will do much to avoid fibrosis and recurrent infection In the early stages frequent elevation of the extremity and assiduous use of elastic bandages or stockings will suffice Focal infection and obvious lesions such as epidermophytosis in the extremity should be eradicated Recurrent lymphangitis is best treated by rest sulfonamide drugs elevation of the extremity and hot moist dressings for comfort with resumed bandaging after the patient is again active Stock or autogenous vaccines and nonspecific protein therapy may be used to increase general resistance to the infective organism In advanced cases with fibrosis and resistant edema the Kondoleon operation and its modifications produce some relief

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CIRCULATORY COLLAPSE AND SHOCK

Failure of the circulation results from a variety of causes The terms circulatory collapse and shock' are applied to circulatory failure in which the heart is not primarily at fault The heart cannot act as an efficient pump unless the venous inflow to it is adequate it cannot pump out blood which it does not receive In peripheral circulatory failure it is assumed that the venous return is inadequate because of some disturbance in the peripheral circulation and that if the venous return were made adequate the heart would function normally Thus from the physiologic viewpoint peripheral circulatory failure may be said to be present whenever the blood flow to the tissues becomes inadequate in the presence of a heart capable of sustaining a normal blood flow Homans summarizes the clinical picture of shock as follows (1) An appearance of pallor sometimes associated with slight cyanosis (2) a cold moist or sweaty skin (3) a rapid regular but thready pulse (4) rapid usually shallow respiration (5) restlessness and an appearance of anxiety which may change under unfavorable circumstances to dulness and lessened sensitiv

As soon as thrombophlebitis is suspected the patient should be kept at rest in bed with the affected extremity elevated to diminish edema Blocking the sympathetic ganglia by the paravertebral injection of procaine abolishes reflex vasospasm relieves pain and diminishes edema Anticoagulants as mentioned above can have no effect on existing thrombi but may be used to prevent propagation Local heat should be applied by means of a thermo regulated cradle Proximal venous ligation should be considered if the thrombus is extending into the thigh is suppurating or if a history of previous pulmonary embolism is obtained There is increasing tendency to shorten greatly the period of absolute bed rest because sluggish blood flow predisposes to development of new thrombi or propagation of the original thrombus

After temperature and pulse are normal the patient may sit up in bed unless activity is followed by return of symptoms or a rise in temperature Passive and later active movements of the affected extremity are started gradually to help recovery of muscle tone and to assist the function of collateral venous channels If edema still forms the limbs should be elevated nightly and when normal activity is resumed an elastic stocking should be worn until measurement of the extremity reveals no accumulation of edema fluid while the tissues are unsupported For relapsing phlebitis foci of infection should be eradicated and if latent phlebitis is itself a focus the responsible vessel should be excised For recurring thrombophlebitis autogenous vaccines are occasionally very useful while stock vaccines or nonspecific protein therapy are generally less effective Brawny swelling and induration may be somewhat relieved by vigorous massage and heat if there has been no recent phlebitis Gross deformity ulceration and infection may require amputation

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DISEASES OF THE PERIPHERAL LYMPHATIC VESSELS

The lymphatic capillaries form a rich intercellular network and collect excess tissue fluid which as lymph is conducted by valved lymph channels of increasing size to regional lymph nodes and thence through trunk lymphatics to the subclavian veins The flow of lymph depends on muscular contraction respiratory movements and to a certain extent on gravity

LYMPHANGITIS

Lymphangitis refers to acute or chronic inflammation usually streptococcic in origin affecting the lymphatic vessels and the immediately adjacent tissues Advancing lymphangitis indicates that infection is spreading and is therefore a danger signal of special importance The path by which bacteria penetrate the skin cannot be discovered in some cases but usually local trauma trichophytosis or chronic ulcers are obvious portals of entry Slightly indurated red tender streaks appear in the skin of the leg or forearm and the regional lymph nodes in the knee, groin or axilla rapidly become swollen and tender Malaise chills fever increased pulse rate and leukocytosis indicate systemic reaction and possible blood stream infection Lymphangitis, always of grave import is especially dangerous in the ischemic tissues of patients with peripheral vascular disease Under these unfavorable conditions prompt high amputation is often required whereas when circulation is normal drainage of the original focus rest hot wet dressings and sulfonamide therapy will usually produce rapid recovery

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LYMPHEDEMA

Lymphedema is a form of chronic bilateral or unilateral edema of the extremities due in its primary form probably to congenital

stimuli from the brain the blood drains into the dilated vessels the venous return to the heart becomes inadequate and arterial pressure falls precipitously The resulting cerebral ischemia may produce unconsciousness As noted below respiratory alkalosis is frequently a factor in producing the loss of consciousness

In the circulatory collapse induced by sodium nitrite or by infection the same two factors are operative namely the force of gravity and the relaxation of the venous side of the circulation In these cases the loss of venous tone is probably the result of the action of the drug or of the infection on the veins and venules. Under such circumstances when the patient is in the upright or sitting position more than the normal amount of blood is pooled in the relaxed venous system and circulatory collapse may result Studies of this type of circulatory collapse have shown that the arterioles are constricted to compensate for the decrease in effective blood volume and that further arteriolar constriction by drugs is not helpful

If the blood volume is decreased by hemorrhage vomiting or loss of plasma into the peritoneal cavity circulatory collapse may occur when the patient sits up In these cases the venous tone may not be decreased When the patient is in the erect or sitting position the shifting of a normal amount of blood into the lower portion of the body may decrease the venous return to the heart sufficiently to produce circulatory collapse

In certain patients a similar type of collapse occurs in the recumbent position Subjects who are bled when they are in the recumbent position may develop collapse which lasts for only a short time and from which they may recover without any demonstrable increase in blood volume Palpation of the abdomen in a patient with acute pancreatitis may repeatedly precipitate collapse In these patients the development of collapse may be of more serious import than in patients in whom circulatory failure is precipitated by gravity

Patients frequently develop circulatory collapse after *spinal anesthesia* This is the result of vascular relaxation in the lower extremities and splanchnic areas This relaxation includes the arterial as well as the venous side of the circulation The dilated vascular bed pools blood and decreases the venous return to the heart

Fainting is not always secondary to the cerebral ischemia which results from a *marked decrease in cardiac output* Many of the stimuli which cause circulatory collapse also produce reflex overbreathing This hyperventilation lowers the carbon dioxide content of the arterial blood and alkalosis results This alkalosis causes a disturbance in cerebral metabolism which may lead to unconsciousness In many instances syncope occurs because of the combined effects of circulatory collapse and respiratory alkalosis.

In the *treatment* of circulatory collapse it is important to make use of gravity in aiding the venous return to the heart. The patient is placed in the *recumbent position* and if possible the foot of the bed is elevated In most instances this will produce a rapid increase in the arterial pressure and the pulse will become of good volume In the treatment of collapse which occurs soon after the induction of spinal anesthesia the head down position is contraindicated if the anesthetic used has a specific gravity greater than that of the spinal fluid The *Trendelenburg position* may be used however after sufficient time has elapsed to allow most of the anesthetic drug to be fixed in the tissues

Drug therapy is frequently not needed because recovery may be quite rapid In patients with severe infection or with a considerable decrease in blood volume recovery of the circulation may be much slower If pain is present morphine sulfate in 15 mg (gr ¼) doses is useful Except in collapse occurring during spinal anesthesia the arterioles are usually constricted and drugs which accentuate this constriction without increasing the venous return are usually ineffective in preventing the onset of collapse In laboratory experiments paredrinol sulfate a drug that increases the venous tone when administered in doses of 25 mg (gr ⅜) intramuscularly or 30 to 50 mg (gr ½ to ¾) orally has been effective in preventing the onset of this type of collapse Epinephrine and pitressin were ineffective During spinal anesthesia ephedrine sulfate

ity, (6) thirst, (7) a variable amount of nausea and sometimes vomiting To this picture there are many exceptions Some patients do not show pallor or lividity, in others the blood pressure is well maintained in still others the heart rate is not increased —indeed it may be slower than normal In other patients mental dulness may be absent Thirst is quite commonly *absent* The rectal temperature may be elevated

There is frequently no clear cut distinction made between collapse and shock It has been suggested that the terms 'primary shock or collapse' be applied to sudden short lived insufficiency of the peripheral circulation, and that the terms ' secondary shock" or shock" be used when the circulatory insufficiency is more prolonged This distinction has not been in general use Nevertheless it is a useful one because the *prognosis* and therapy of sudden transitory insufficiency of the circulation is frequently different from that of more prolonged peripheral circulatory failure. The term ' collapse ' is preferred to primary shock because it is more general Primary shock associated with wounds is one type of collapse In this discussion the term peripheral circulatory failure will include all examples of generalized circulatory failure in which the heart is capable of functioning normally Circulatory collapse will include all forms of *sudden*, short lived peripheral circulatory failure, shock" will include the cases of peripheral circulatory failure of longer duration

The Mechanism of Peripheral Circulatory Failure—Investigators agree that the fundamental mechanism of peripheral circulatory failure is a disproportion between the circulating blood volume and the size of the vascular bed This disproportion may occur in two ways because of (1) a decrease in the circulating blood volume so that the vascular bed is not adequately filled and (2) an increase in the size of the vascular bed so that the normal blood volume does not fill the dilated vascular bed This vasodilatation may result from fever infection or drugs or it may be of reflex origin In any case the venous return to the heart becomes inadequate and the cardiac output decreases

Circulatory Collapse—Acute transient peripheral circulatory collapse is very common It may occur in normal subjects at the *sight of blood* during a venepuncture or if the subject is hurt or becomes nauseated It *frequently occurs* in ambulatory patients who have had a cold or infection in the hospital it is seen in patients with pneumonia or other infections who sit up to use the bed pan or in persons who stand up too soon after a bout of fever or after the loss of blood It occurs from time to time when acutely ill patients are moved, or it may be precipitated by palpation of a tender abdomen

Regardless of the *precipitating cause*, the *clinical picture* is the same The patient becomes deathly pale, breaks out in a cold sweat, and complains of epigastric distress and nausea The field of consciousness becomes narrowed, objects become hazy and dark and the subject may lose consciousness At the onset of the attack the heart rate usually becomes rapid but as the arterial pressure falls the heart rate frequently decreases At the height of the collapse the heart rate may be approximately 40 and the radial pulse impalpable If the subject is held in the upright position he may develop clonic movements of the arms and legs

Circulatory collapse in these cases results primarily from *pooling of blood* in a dilated circulatory bed The blood volume is not decreased in the normal subject with circulatory collapse precipitated by *unpleasant* visual stimuli pain or nausea The marked fall in arterial pressure indicates that the peripheral vascular bed has dilated so that the normal blood volume no longer fills the dilated vascular bed and the venous return to the heart becomes inadequate There are two factors operative in this type of collapse The first one is gravity, the second is the stimuli to the central nervous system When the patient is in the upright or sitting position the venous pressure in the parts of the body below the heart is increased by the force of gravity This increased venous pressure makes the cross section area of the venous bed below the heart larger when the patient is in the upright position than when he is in the recumbent position When the tone of these vessels below the level of the heart is suddenly decreased as a result of

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In certain patients a similar type of collapse occurs in the recumbent position. Subjects who are bled when they are in the recumbent position may develop collapse which lasts for only a short time and from which they may recover without any demonstrable increase in blood volume Palpation of the abdomen in a patient with acute pancreatitis may repeatedly precipitate collapse In these patients the development of collapse may be of more serious import than in patients in whom circulatory failure is precipitated by gravity

Patients frequently develop circulatory collapse after *spinal anesthesia* This is the result of vascular *relaxation in* the lower extremities and splanchnic areas This relaxation includes the arterial as well as the venous side of the circulation The dilated vascular bed pools blood and decreases the venous return to the heart.

Fainting is not always secondary to the cerebral ischemia which results from a *marked decrease in cardiac output* Many of the stimuli which cause circulatory collapse also produce reflex overbreathing This hyperventilation lowers the carbon dioxide content of the arterial blood and *alkalosis results This alkalosis causes a disturbance* in cerebral metabolism which may lead to unconsciousness In many instances syncope occurs because of the combined effects of circulatory collapse and *respiratory alkalosis.*

In the *treatment* of circulatory collapse. it is important to make use of gravity in aiding the venous return to the heart. The patient is placed in the *recumbent position* and if possible the foot of the bed is elevated In most instances this will produce a rapid increase in the arterial pressure and the pulse will become of good volume In the treatment of collapse which occurs soon after the induction of spinal anesthesia the head down position is contraindicated if the anesthetic used has a specific gravity greater than that of the spinal fluid The *Trendelenburg position* may be used however after sufficient time has elapsed to allow most of the anesthetic drug to be fixed in the tissues

Drug therapy is frequently not needed because recovery may be quite rapid In patients with severe infection or with a considerable decrease in blood volume recovery of the circulation may be much slower If pain is present morphine sulfate in 15 mg (gr ¼) doses is useful Except in collapse occurring during spinal anesthesia the arterioles are usually constricted and drugs which accentuate this constriction without increasing the venous return are usually ineffective in preventing the onset of collapse In laboratory experiments paredrinol sulfate a drug that increases the venous tone when administered in doses of 25 mg. (gr ⅜) intramuscularly or 30 to 50 mg (gr ½ to ¾) orally has been effective in preventing the onset of this type of collapse *Epinephrine and pitressin* were ineffective During spinal anesthesia ephedrine sulfate

given subcutaneously in doses of 25 to 50 mg (gr ⅜ to ¾) is at least partially effective in preventing a drop in blood pressure Altschule and Gilman have reported that paredrine given intramuscularly in doses of 10 to 20 mg is likewise effective in preventing a drop of blood pressure during spinal anesthesia

Shock—More prolonged failure of the peripheral circulation produces the classical clinical picture of shock In collapse the duration of the circulatory insufficiency is short, in shock it is more prolonged It is generally agreed that in shock the circulatory failure is frequently related to a decrease in blood volume as a result of external hemorrhage dehydration or loss of plasma into the peritoneal cavity or into traumatized tissues In addition many observers believe that infection and the breakdown products from injured tissues play an important role not only in causing pooling of blood by vasodilatation but also in producing a decrease in plasma volume by increased capillary permeability Monographs by Blalock Cannon Moon Scudder and Wiggers give reviews of the current opinions on etiology of shock

When the circulatory failure is caused by dehydration the administration of physiologic saline restores the plasma volume to normal and the circulation improves If protein is lost from the plasma either as a result of hemorrhage or of increased capillary permeability at the site of a burn or injury the administration of physiologic saline may not restore the plasma volume to a level adequate to maintain a normal circulation In the case of hemorrhage transfusion of whole blood is indicated In the case of plasma loss into injured tissues plasma is needed The loss of plasma into the tissues may be lessened by external pressure or by cooling the part Elevation of the foot of the bed aids the venous return to the heart Infection should be prevented, or if present it should be combatted by appropriate chemotherapy Pain is controlled by the administration of morphine Usually the administration of sympathomimetic drugs is of little therapeutic value even though a transient rise in blood pressure may be obtained

All observers in World War I emphasized the importance of keeping the patient warm and in the case of broken bones the necessity for splinting and immobilization before moving the patient In certain patients however it may be useful to cool an injured extremity This decreases the metabolism of the cells and lowers the blood flow As the blood flow decreases, less protein leaks through the injured capillaries into the traumatized tissues In civilian practice the importance of treating shock before moving the patient for roentgen ray examination or before undertaking any operative procedure is universally recognized Cannon stresses the importance of restoring the blood volume before using an anesthetic and points out the danger of even slight anoxemia in cases of shock

Terminal Circulatory Failure—If trauma is severe enough or if infection cannot be controlled the circulation eventually fails regardless of treatment In this terminal picture hemoconcentration plays little part because it will occur even if the blood volume is maintained by continuous transfusion The relative importance of the central nervous system of the peripheral vascular system and of the heart in this terminal picture is not clear This problem needs to be elucidated by more clinical observations

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DISEASES OF THE DUCTLESS GLANDS

INTRODUCTION

The author won't write the conventional introduction. He won't give the Greek derivation for the word "hormone" coined by Starling; he won't discuss the experiments of Claude Bernard which lead to the conception of an internal secretion; he won't delve into the earliest beginnings of Endocrinology which had as their *raisons d'etre* such ends as the procurement of manpower for the harem, the salvaging of a male soprano voice for the choir, the increased palatability that a rooster attains when he turns into a capon, and so on; he won't trace experimental Endocrinology from 1849 when Berthold studied the effect of the gonads on the secondary sex characteristics of fowl down to the present 1943 when Reichstein synthesized corticosterone from the author knows not what (military "secret"!); no, he won't even list the names of describers of various endocrine syndromes—Addison with Addison's Disease in 1855 down to, shall we say, the almost simultaneous elucidation of hyperparathyroidism in 1928 by Mandl and Du Bois.

Instead, he will discuss what is Endocrinology with special emphasis on what is not Endocrinology and then will comment on certain other aspects of the subject.

What Is Endocrinology?—Endocrinology is an indivisible division of Internal Medicine and has to do with certain glands or tissues which secrete highly specific substances into the blood stream for use by other tissues. The only important thought in the above definition is contained in the word "indivisible." It is impossible to separate Endocrinology from Internal Medicine; by the same token it is impossible to be an endocrinologist without being an internist. The physician who calls himself an endocrinologist and confines his interests to such unfortunate members of society as might appear in the sideshow of a circus never realizes that pneumonia, a broken leg and a bad burn involve important changes in adrenal cortical function (cf. "Alarm Reaction" of Selye); that the disturbance in homeostasis occasioned by chronic renal insufficiency is ameliorated by a secondary hyperparathyroidism; that the somatotropic action of testosterone propionate may be made use of in many conditions other than male hypogonadism, and so on.

The author resents the tendency to limit the scope of Endocrinology to those disorders of the internal secretions which are not clearly understood. Thus once some division of Endocrinology such as diabetes is put on a firm footing, it is removed from the section on Endocrinology to the section on Metabolic Diseases.

What Isn't Endocrinology?—Certain conditions often considered to be endocrinological are probably not so at all.

First in order of frequency comes the fat boy who is slightly late in sexual development and whose genitalia are obscured by excess of fat. This patient, nine times out of ten, is labeled as Fröhlich's Syndrome, whereas in point of fact he is just a fat boy, whatever that is. If left alone, he will develop normally sexually and very frequently will cease to be fat after puberty. True Fröhlich's Syndrome is exceedingly rare and difficult to diagnose before the age of normal onset of puberty.

Then there comes the child that does not do well in school. There is a feeling among would-be progressive educators that such a situation demands a survey by an endocrinologist. In the author's experience there is only one endocrine abnormality which leads to mental retardation, namely cretinism. The diagnosis of this condition is a problem for the obstetrician and the pediatrician, not for the endocrinologist. If it is not made in the first few weeks or at the most, months of life, the damage is already done and one might just as well not make the diagnosis. Parenthetically it might be added that every physician should suspect cretinism in any child with an umbilical hernia at birth which persists after the first few weeks of life. Even juvenile myxedema is not asso-

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ciated with retarded mentality To be sure long standing hypoparathyroidism leads to epileptic seizures and secondary mental retardation The author has seen in consultation a number of children with poor school records and to date has been unable to make an endocrinologic diagnosis on any of them He is impressed by the fact that many of them have been mirror readers'

A third type of case sent to the endocrinologist is the patient with some congenital disorder of the germ plasm such as mongolian idiocy Laurence Moon Biedl syndrome and so on Just why such conditions should be confused with endocrinopathies is not very clear It is probably connected with the belief (v supra) that anything which is not fully understood belongs to Endocrinology

Finally there are the patients with alopecia areata The endocrines have something to do with certain types of hair these patients have too little hair therefore they are sent to the endocrinologist However the fact that this condition starts by being spotty is strong evidence against an endocrinologic etiology It makes no difference that one spot may enlarge to the point where it covers the whole body the disease is still a spotty one Endocrinologic diseases are generalized not localized hormones do not stop in the midline or proceed down one limb and not the other, etc For example Paget s disease of bone is not *endocrinologic since it is not generalized* Though it involves 95 per cent of the skeleton, there will still be a sharp demarcation between the uninvolved part and the Paget s disease Postmenopausal osteoporosis on the other hand may be confined to the spine and pelvis and still be a generalized disease since here there is a rhyme and a reason to the distribution This discussion concerns the *primary* lesion produced by an endocrinopathy Secondary complications can be *spotty* (*e g* gangrene of the toe in diabetes bone cyst with hyperparathyroidism)

Failure of End Organs to Respond to Hormones—Since a hormone acts somewhere it is obvious that one might get very much the same clinical syndrome from failure of the end organ to respond to the hormone as one would get with absence of the hormone itself For example let us take pseudohypoparathyroidism Patients with this condition have the clinical and chemical findings that one associates with hypoparathyroidism but *they fail to respond* to parathyroid hormone and their parathyroid glands not only are not absent but may be hyperplastic (unpublished data) A second example is the failure of the American Indian to develop a beard Recently a patient presented himself his only complaint being failure to develop a beard Elaborate studies were carried out with uniformly normal results Finally some one had the wit to inquire about the patient s ancestry and *found that he was part Indian*

A Caution as to the Use of Pituitary Extracts—Because of the danger of antibody formation the author disapproves of the parenteral use of pituitary extracts He may be overconservative in this respect There is considerable evidence however that these extracts which contain proteins are strongly antigenic this results in the formation of antibodies which inhibit the further action of the injected hormone This in itself would not be so bad if it were not for the fact that the antibodies may also neutralize the patient s own pituitary hormones Dr Kenneth W Thompson at Yale has a dog named Alice which received pituitary extracts and which developed many of the symptoms of panhypopituitarism Other dogs similarly treated developed this same syndrome and showed at autopsy large pituitary glands which *from their histological appearance* (castration and thyroidectomy cells) were in all probability producing an excess of pituitary hormones This word of caution does not apply to chorionic gonadotropin which is strongly antigenic in rabbits but not in man presumably because its origin from the human placenta makes it homologous When a satisfactory preparation of follicle stimulating hormone is obtained from the urine of women after the menopause it too will probably be safe to use

Oophorectomy—The author feels that needless oophorectomy constitutes one of the greatest faults in medical practice A normally functioning ovary *needless to say* is most essential for the future physical and mental well being of a young woman Satisfactory as replacement therapy is it will not produce ova or be a substitute for mother-

hood There are two chief reasons for unnecessary ovarian surgery

The general surgeon does not realize that the normally functioning ovary is a cystic organ he performs an exploratory laparotomy for some sort of abdominal pain and finds nothing but cystic ovaries out they come For some reason the surgeon is never sued for malpractice because of this the story would be very different if under somewhat analogous conditions castration was resorted to in the male *Metropathia hemorrhagica* is the second big cause for unnecessary removal of the ovaries This interesting condition can be treated medically in almost all instances.

Even after the menopause the author disapproves of oöphorectomy He feels that the ovary still functions to a certain extent after the periods have ceased and that one sees more severe osteoporosis following an artificial menopause than after a physiologic one

Fat Distribution —Considerable space has been wasted in textbooks and writings on endocrinology about the distribution of fat. In the writer s opinion there are fat people and thin people but with one exception the distribution of fat is of no diagnostic significance The one exception is in Cushing s Syndrome where there is a tendency for the face to be round (moon faced) this roundness is probably due to a tendency to deposit fat in this region However that a propensity to deposit fat around the hips or on the lower extremities or diffusely throughout the body or where you will has any diagnostic significance is most unlikely it almost certainly has nothing to do with pituitary disease

Practical versus "Theoretical" Knowledge —The subject matter of this paragraph is applicable to all Internal Medicine but especially to Endocrinology The author is frequently asked in giving a talk to make it practical and not too theoretical By practical is usually meant therapeutic by theoretical is usually meant fundamental The author has no patience with such a philosophy One cannot possibly practice good medicine and not understand the fundamentals underlying therapy Very few of any rules for therapy could be more than 90 per cent correct If one does not understand the fundamentals one does more harm in the 10 per cent of instances where the rules do not apply than one does in the 90 per cent where they do apply The same policy carries over to medical education There are those who advocate medical schools which will turn out practical physicians rather than theorists. But they end by turning out a poorer grade of doctors and as in the case of eggs there is no such thing as a poor doctor, they are either good or bad

Fuller Albright

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DISEASES OF THE THYROID GLAND

Clinical classification

Colloid goiter simple goiter struma Large thyroid acini overfilled with colloid

Adenoma Nodular goiter Benign tumor in the thyroid gland

(a) *Without systemic effects*

(b) *With hyperthyroidism* toxic adenoma

Exophthalmic goiter Graves disease Basedow s disease thyrotoxicosis hyperthyroidism

Thyroiditis Acute or chronic inflammation of the gland

Myxedema Diminished activity of the thyroid in adults hypothyroidism

Cretinism Inadequate activity of the thyroid in children with retardation of growth

Malignant disease

The Committee on Classification of the American Association for the Study of

Goiter has recommended the following tentative clinical classification

Type 1 Nontoxic diffuse goiter
Type 2 Toxic diffuse goiter
Type 3 Nontoxic nodular goiter
Type 4 Toxic nodular goiter

This is a simple grouping based on easily recognizable signs and symptoms but it has not yet been generally adopted The chief thing to remember is that simple goiter may be diffuse or nodular and that hyperthyroidism may occur in a gland with or without nodules

The various manifestations of diseases of the thyroid gland are greatly simplified if we consider them in the light of our knowledge of the function of this organ It serves *as a storehouse of iodine and elaborates* iodine containing substances the most important being thyroglobulin and the hormone thyroxin which have a controlling influence on growth and metabolism Recent work has shown that the thyrotropic hormone of the anterior lobe of the pituitary has an influence on thyroid activity There is an interrelationship between all of the ductless glands

As might be expected diseases of this gland are most frequent in districts where the iodine content of food and water is low but this deficiency is not the only factor as many cases appear in regions where iodine is abundant Webster lists the important conditions which increase the need of the body for thyroxin and therefore increase the iodine utilization (1) pregnancy (2) puberty (3) infectious diseases (4) Graves disease (5) pituitary disorders which bring about an increased secretion of the thyrotropic hormone (6) foods which depress tissue oxidation and thus increase the demand for thyroxin as in the simple goiter produced by the injection of cyanide or the feeding of cabbage and other vegetables with a high content of this goitrogenic substance If for any reason the iodine content of the gland falls below the normal minimum (0 1 per cent of dry substance) the organ is stimulated its blood supply is increased and the cells lining the alveoli hypertrophy Hyperplasia of the cells follows with infoldings which fill the spaces left by the decreasing colloid material Usually involution to the normal gland structure takes place with some increase in size If the previous hyperplasia has been marked typical colloid goiter results with large alveoli distended with colloid Occasionally physiologic exhaustion sets in with resulting atrophy If stimulated by thyrotropic hormone or some other substance the gland instead *of involuting* may develop a greatly increased blood supply with many infoldings of hyperplastic cells which replace the diminishing poorly staining *iodine-impoverished* colloid As a result of this glandular stimulation hyperthyroidism develops

Eugene F DuBois

COLLOID GOITER

Definition —Colloid or simple goiter is an enlargement of the thyroid gland generally diffuse and symmetric sometimes nodular which usually starts at the age of puberty The alveoli of the gland are distended by an excessive deposit of colloid The function is normal and the symptoms due merely to enlargement

Occurrence —Goiter is common in certain *mountainous regions* and on the sites of old glacial ice fields The incidence is high in some of the valleys of the Alps Pyrenees and Himalayas also in parts of Austria southern Germany and England In North America it is found chiefly in the northwest in the Great Lakes Basin and in the valley *of the upper Mississippi The examination* of recruits for the first World War showed that twenty one to twenty seven individuals per 1000 were affected in the states of Idaho Oregon Washington and Montana while along the eastern seacoast only two to five per 1000 had simple goiter

Etiology —The disease was *familiar* to the ancients as might be expected from its striking characteristics Its association with the water supply has long been recognized even by savage tribes although definite proof was lacking until the brilliant studies of Marine and his co workers demonstrated that this form of goiter is *due to an absolute* or relative *deficiency of iodine* in the water and food Analyses have proved that goiter *may* sometimes affect as many as half the inhabitants in the parts of our country where the water and local vegetables contain little

iodine. And this has been found to be true in other goitrous regions of the world Such districts are usually rather far inland and it may be supposed that the iodine has been leached out of the soil Near the seacoast iodine is abundant in the water and plants and goiter is therefore relatively uncommon

Certain it is that Marine and his associates have been able to reduce tremendously the incidence of goiter in some of the lake district states by administering to school children small doses of iodine twice a year Even more striking results are being obtained in Switzerland

Preventive treatment should be applied especially to girls since goiter is about five times more common in females than in males The swelling of the neck usually makes its first appearance at the time of puberty and tends to disappear by the age of twenty five or thirty There is a distinct relationship to the *sex glands* and the enlargement may increase with menstruation or pregnancy It is particularly important that pregnant women should have a sufficient supply of iodine in order to prevent cretinism in the offspring

Morbid Anatomy—In colloid goiter the thyroid gland is diffusely enlarged It is firm and on section is of a reddish amber color and contains acini distended with colloid On microscopic examination it is found that the acini vary greatly in size most of them being distended with normally stainable colloid The epithelial cells are of low cuboidal shape and there may be spriglike projections which are the remnants of previous infoldings of epithelium Marine believes that in these glands there has been first a diminished iodine store and second a period of stimulation with hyperplasia The colloid stage is a resting phase in which the function of the gland is practically restored to normal Adenomas are frequently present in colloid goiter causing one or more nodules Other nodules may be formed by large cysts with areas of calcification In some instances the enlarged gland presses on the neighboring organs obstructs the trachea and extends downward into the thoracic cavity The percentage of iodine contained in the goitrous gland during the resting stage may be normal but is usually diminished The functional ability of the gland is also usually normal but some patients give evidence of a slightly diminished thyroid secretion

Symptoms—Enlargement of the neck is the first noticeable sign Later there may be a sense of fulness and if there be pressure on the trachea difficulty in breathing during exertion As a rule the gland is firm and symmetrically enlarged though it may be nodular and asymmetric on account of adenomata Occasionally patients are seen in whom the swelling causes a most unsightly disfigurement Constitutional symptoms are lacking and the basal metabolism is almost always within normal limits Simple goiter rarely develops into Graves disease or myxedema

Diagnosis—Confusion in diagnosis sometimes results from the combination of a diffuse colloid goiter and effort syndrome (neurocirculatory asthenia) or some other nervous manifestations resembling *exophthalmic goiter* The differentiation can be made by a careful analysis of the symptoms with especial attention to the pulse rate during complete rest or sleep A determination of the basal metabolism is of great help The *adenomas* can be distinguished from diffuse goiter by the presence of nodules but it must be remembered that many nodules are chiefly colloid material some true benign adenomas and some malignant

The possibility of *intrathoracic goiter* should always be borne in mind if there are any symptoms suggesting the presence of an abnormal mass beneath the manubrium

Prophylaxis—Preventive treatment should be used in all regions in which endemic goiter is prevalent Iodine may be added to the drinking water or to the table salt in the proportion of 10 mg of potassium iodide per kilogram of table salt There is an objection to the generalized treatment of a community on the ground that it is wasteful and some physicians still believe that if too large an amount is used it may result in the production of hyperthyroidism in predisposed adults A better plan is the individual administration of chocolate tablets* containing 5 to 10 mg of iodine once

* Examples of these are Tablets Iodo-Casein with Chocolate (Mulford) N.N.R and Chocolate Tablets Iodostarine-Roche, N.N.R. Each tablet contains 0 01 Gm iodine

a week or 1 or 2 ounces of syrup of hydriodic acid in divided doses given twice each year Means uses as prophylactic 1 drop of Lugol's solution once a week The most important groups to treat prophylactically are pregnant women particularly those who have had goiter in adolescence, and school children especially the girls

Treatment —In America the simple goiter found in young people usually increases in size for several years and then decreases until by the age of twenty five it has almost disappeared Treatment with iodine sometimes helps regression in the young but the results are disappointing in older subjects This treatment may diminish the colloid portions of a large struma causing the adenomas to become more apparent

The advisability of preliminary treatment with thyroid has been questioned but some believe that with young subjects the best results are obtained by using first the standard U S.P desiccated thyroid* in doses of 1½ to 3 grains (0 1–0 2 Gm) daily for a period of two weeks if there has been no change in pulse or weight or other evidences of hyperthyroidism the same treatment may be repeated Then after an interval of one or two weeks small doses of iodine are started for example 30 to 60 minims (2–4 cc) of syrup of hydriodic acid daily for two or three weeks The treatment should be repeated three times during the year Large amounts of iodine may cause at first such a rapid accumulation of colloid in the gland that it becomes firm and painful

Surgical removal is desirable if there be much deformity or any serious pressure

Eugene F DuBois

* Lugol s Solution Compound Solution of Iodine U.S.P contains iodine 5 per cent and potassium iodide 10 per cent One cc of Lugol s Solution contains 126.5 mg of iodine

Syrup of Hydriodic Acid contains about 1 4 per cent of hydriodic acid One cc contains about 14 mg of iodine

Thyroid U S P Desiccated Thyroid Glands contain about 0 2 per cent of iodine (0 17–0 22 per cent)

Means has found that it makes little difference what form of iodine is given except, of course in the thyroid preparations Comparing these preparations in his experience the following are of equal calorigenic effect in myxedema patients 1½ grains (0 1 Gm) of U S P (Armour Lederle Lilly etc) thyroid 1 grain (0 065 Gm) of Parke Davis thyroid 5 grains (0 3 Gm) of Burroughs Wellcome thyroid or 0.35 mg of pure thyroxin

ADENOMA

Adenomatous enlargement of the thyroid gland usually causes no constitutional symptoms, but in certain cases is associated with hyperthyroidism

Morbid Anatomy —There are in the thyroid tissue rests which probably represent an excess of thyroid not ordinarily needed by the organism Normally these are slowly destroyed but under certain stimuli they react and grow Most of these rests are of the adult type having been fully differentiated others remain fetal in type When the whole gland is stimulated by lack of iodine these fetal rests may develop into adenomas of a type which depends upon the differentiation of the cell rest at the time of stimulus They may pass through the stages of hypertrophy and hyperplasia and then either atrophy or by involution reach the colloid resting stage The anatomic picture, therefore depends upon two factors the developmental stage of the original cell rest and the stage of activity of the adenoma The picture is further complicated by the fact that the term *adenomatous growth* includes a range of conditions extending from a more or less diffuse uniform hyperplasia to a well defined encapsulated mass As a rule adenomas of the adult type (simple adenomas) have poorly developed capsules Fetal adenomas which are benign growths are more frequently multiple resembling large lymphoid foci they contain no visible colloid and the stroma is scanty An intermediate type between the adult and the fetal also occurs All three types of adenomas grow from a subcapsular zone and since their blood supply comes from the periphery the nutrition of the central portions may be impaired There is a tendency toward necrosis and the formation of cysts

Symptoms —A growing lump in the neck may be the first sign noted by the patient but more often the growth takes place in a gland which has previously been enlarged On examination the mass is rounded rather firm perhaps a little tender Often several masses are palpable some of them nodular due to the fusion of adenomas They are not adherent to the skin or deeper structures Sometimes the adenomas become apparent only when the enclosing mass of diffuse goiter has decreased in size as the result of

treatment Often they are first discovered by the pathologist in tissue removed at operation In most cases constitutional symptoms are lacking

Treatment.—Most adenomas produce no symptoms except mild disfigurement and pressure A small number become toxic a very small percentage malignant Surgical removal is desirable but not imperative except for severe pressure or toxicity or suspicion of malignancy Removal of the adenomas is not difficult Some patients improve with the administration of desiccated thyroid

Plummer called attention to a group of *hyperfunctioning adenomatous goiters* (*toxic adenomas*) in which symptoms of hyperthyroidism may occur usually between the ages of thirty five and forty The onset of the constitutional symptoms is often without apparent cause but it may be initiated by the administration of iodine and once started continues even after the iodine has been withdrawn The patient, at the time of examination gives a history of having had a swelling of the neck for many years There has been a gradual onset of the symptoms of hyperthyroidism with a rising *basal metabolic rate* which reaches an average of about 30 per cent above normal *Exophthalmos* seldom occurs possibly because this distressing symptom is infrequent in patients who develop hyperthyroidism after the age of thirty five Rapid recovery follows removal of the adenoma Unless cardiac damage has become too serious operation should be urged as the prognosis is good after removal of the hyperfunctioning adenoma

The opinion of the medical profession regarding the clinical aspects of adenomas and "toxic adenomas has been changing during the past few years This is well exemplified in the 1931 report of the Committee on Classification of the American Association for the Study of Goiter which places the adenomas under the headings nontoxic nodular goiter and toxic nodular goiter At one time it was thought that exophthalmic goiter and toxic adenoma showed distinct differences in etiology symptomatology course and response to treatment Most observers now feel that there is no essential difference between exophthalmic goiter and toxic adenoma but that they are clinical variations of a single disease The writer shares this view

EUGENE F DUBOIS

EXOPHTHALMIC GOITER

(*Graves Disease Basedow s Disease Thyrotoxicosis Hyperthyroidism*)

Exophthalmic goiter is a disease of unknown etiology occurring in constitutionally predisposed individuals It is associated with a diffuse, parenchymatous hypertrophy and hyperplasia of the thyroid gland with an excessive and possibly abnormal thyroid secretion The clinical manifestations result largely from an increased metabolism of the cells of the body and a disturbance of the autonomic nervous system

History —Exophthalmic goiter was first described by Parry but the published account in his posthumous papers attracted little attention and the first well known publication is that of Graves in 1835 A few years later Basedow gave a good account of the condition In English-speaking countries it is usually called Graves disease and on the continent, *morbus basedowi* Moebius suggested that the cause was a pathologic activity of the thyroid gland and contrasted the disease with myxedema which is due to a loss of function of the thyroid Friedrich Muller in 1893 recognizing the increased protein destruction called attention to the probability of an increased total metabolism This was proved two years later by Magnus-Levy who found that the oxygen consumption was above normal in exophthalmic goiter and below normal in myxedema. He later showed that the severity of exophthalmic goiter is roughly proportional to the basal metabolism In severe cases the metabolism is 70 per cent or more above normal and in moderately severe cases 20 to 50 per cent above. The determination of the basal metabolism was used but little as a clinical method until 1916 when a series of studies in America made it applicable to the clinic Since that time there has been a marked improvement in the accuracy of diagnosis and a simplification of the literature of diseases of the thyroid Kendall isolated thyroxin an active principle of the gland in 1915 Harington and Barger synthesized thyroxin in 1927 Aub and his co-workers have shown that the rate of calcium phosphorus metabolism is increased in hyperthyroidism and decreased in myxedema

Etiology —Exophthalmic goiter is apparently a disease of civilization occurring most frequently among young adults in cities where life is strenuous and especially in people of narrow frame light skeletal structure and nervous temperament Women are much more often afflicted than men In a large percentage of cases nervous shock or strain plays an important role and cures are difficult until this strain has been relieved

Most of the symptoms are the direct result of a hypersecretion of the thyroid All of the phenomena, except exophthalmos and certain nervous manifestations have been reproduced in animals by the administration of thyroid substance Overdosage with thyroid in man has given similar results Extirpation of the thyroid in animals and man has caused myxedema which is almost the antithesis of hyperthyroidism There is slight evidence pointing toward an alteration in the nature of the thyroid secretion rather than a mere quantitative increase but some authorities have gone so far as to call the disease dysthyroidism



Fig 154 —Exophthalmos in Graves disease

Pathology —The thyroid gland is diffusely enlarged but sometimes one lobe is bigger than the other It is soft and very vascular and the blood vessels are enlarged The acini show hypertrophy hyperplasia with infoldings of the cells filling up the space left by the greatly diminished and poorly staining colloid Palmer and his associates have shown that the thyroxin thyroglobulin and total iodine content of the untreated gland is below normal but can be increased even above normal by the administration of iodine The extent of the changes in the gland is not always proportional to the severity of the symptoms and in some instances the visible evidences of increased activity are slight

In two thirds of the severe cases there is enlargement of the thymus The heart is usually enlarged In some fatal cases myocardial damage and nutritive change in the cervical sympathetic nerves may exist In one third of the cases adenomas are also present In extreme cases there is great wasting of the body If exophthalmos has existed for some time there may be an increase in the retrobulbar fat Diffuse lymphoid hyperplasia is a constant finding The blood shows an increase in the percentage of lymphocytes and to a lesser extent of the monocytes generally in proportion to the severity of the illness The skeletal muscles especially the muscles of the eye show fatty infiltration Accompanying these muscle changes there is a marked increase in the excretion of creatine The cholesterol content of the blood is low

Symptoms —The patient's complaints are variable Often there is an increasing sense of *fatigue* with nervous excitability and loss of weight In spite of increasing weakness there may be an inward drive urging the patient to purposeless activities An abnormal *appetite* with a sense of warmth and increased perspiration may be noticed *Palpitation* is often the first symptom to attract the patient s attention Sometimes an irritating *cough due to pressure* on the recurrent laryngeal nerve leads to the suspicion of tuberculosis Rarely there are no subjective symptoms until the onset of gastro intestinal crises or cardiac failure

In typical exophthalmic goiter the patient has a peculiar staring expression with brilliant eyes and flushed face and makes many purposeless movements On examination it is found in most cases that the thyroid is enlarged and soft enlargement being as a rule symmetric The gland is sometimes so vascular that the thyroid arteries may be felt and the stethoscope usually reveals a whirring sound called *bruit de diable* The eyes may be so protruding that a rim of white sclera is seen between *the upper* lid and the cornea (*exophthalmos* protrusio bulbi) the lids themselves are usually puffy The patient winks seldom (Stellwag s sign) there is a weakness of convergence (Moebius' sign) and on looking downward the upper lid follows slowly or not at all (von Graefe s sign) The cause of these peculiar ocular manifestations is not known

There is a *fine tremor* of the hands the *skin* is unduly warm and moist and the *heart* beats rapidly with a slapping thrust on the chest and the sounds are of poor muscular quality Sometimes there is distinct cardiac enlargement with relative insufficiency of the valves The pulse pressure *is usually increased due to the rise in systolic* pressure

The *nervous manifestations* may be marked A change in disposition with unwonted irritability and unexpected losses of temper may bewilder the family True psychoses occasionally intervene but as a rule the patients are easily managed once the condition is recognized The cause of the attacks of vomiting and diarrhea which may be alarming is not known Involvement of the autonomic nervous system may be responsible

Most of the symptoms are referable to increased thyroid secretion which stimulates the resting metabolism of all the cells so that the basal metabolic rate is increased roughly in proportion to the severity of the disease Since the oxidations are excessive even while the individual is resting the heart must beat faster in order to supply the tissues with blood Since the body produces more heat than normal each square centimeter of skin must radiate an excessive amount of heat. This accounts for its warmth and perspiration Excessive combustion calls for a greater food intake and if the appetite is not proportionally increased there is a loss of weight The muscles are inefficient they tire rapidly and a given task is accomplished only through the expenditure of an abnormal amount of energy It is easy to see why the continual acceleration of metabolism night and day exhausts the heart and causes great nervous and physical fatigue

In severe cases of exophthalmic goiter the symptoms may develop rapidly causing marked prostration The basal metabolism is increased 75 to 125 per cent or more above normal The heart rate becomes very rapid and auricular fibrillation frequently intervenes Gastro intestinal and nervous manifestations may be prominent these attacks often being precipitated by intercurrent disease or excitement or operation The prognosis then becomes exceedingly grave and death may result from exhaustion In moderately severe cases when the metabolism is 40 to 75 per cent above normal the patient remains an invalid for several years The heart may be seriously damaged and fibrillation may appear The four classic symptoms exophthalmos, goiter tachycardia *and tremor are not necessarily present* but almost invariably some nervous manifestations and the increased metabolism with resulting rapid heart action can be demonstrated In mild cases of the disease when the metabolism is less than 40 per cent above normal there may be few symptoms The characteristic eye signs may be absent or so slight as to attract little attention The thyroid enlargement may be scarcely noticeable Some of the nervous manifestations some weakness tremor and tachycardia will probably be present These cases are often diagnosed as tuberculosis or neurasthenia until the true nature of the malady is discovered They tend to recover early if treated by rest but may progress rapidly in an unfavorable environment In all patients who have suffered from exophthalmic goiter there is danger of recurrence even after operation They may return to active life but seldom to robust health

Complications —The *focal infections* in tonsils or sinuses may demand treatment *Acute infections* are of considerable importance since they increase temporarily the severity of the disease *Glycosuria* occurs in 1 to 2 per cent of the patients, being augmented by carbohydrate food In most of these patients this is merely a spilling of sugar by the kidney and it does not necessarily indicate a diminished power to oxidize True *diabetes* is sometimes a complication and increases the difficulty of treatment There is no specific cardiac lesion but patients whose hearts have been damaged by *rheumatic fever or syphilis or arteriosclerosis* are prone to develop serious cardiac symptoms in hyperthyroidism Fibrillation is a prominent feature often transient often disappearing spontaneously after thyroidectomy

Diagnosis —Errors in diagnosis are frequent *Early pulmonary tuberculosis* may be accompanied by nervousness rapid pulse and loss of weight *Effort syndrome* (neurocirculatory asthenia) may cause the same

symptoms with the addition of vasomotor instability There is another puzzling group of cases with the nervous manifestations of exophthalmic goiter but *without the increased metabolism* a condition that has been called *larval hyperthyroidism* or *forme fruste* Its relationship to exophthalmic goiter is not yet clear Sometimes patients with colloid goiter or adenoma are falsely suspected of hyperthyroidism More and more cases are reported in which an unsuspected thyrotoxicosis has caused cardiac decompensation The diagnosis is suggested by a persistently rapid heart rate that does not respond well to digitalis The recognition of the true etiology is of great importance because in many of these patients relief can be obtained only after thyroidectomy

In guarding against errors nothing is more important than a careful history physical examination and analysis of symptoms The *pulse rate* during sleep or complete rest is as a rule more accelerated in hyperthyroidism than in the other diseases A determination of the *basal metabolism* by one of the comparatively simple machines now used in many clinics is of great value as an aid in diagnosis but only as an aid At the present time many of the metabolism tests are faulty sometimes it is the technic but more often it is the apprehension of the patient that gives results far above the true basal The first test is often unreliable There are a few conditions such as fever leukemia and pernicious anemia which cause a rise in the resting metabolism similar to that of hyperthyroidism but these are readily differentiated Generally the rise in the basal metabolic rate is proportional to the degree of hyperthyroidism but it may be relatively slight in some patients whose cardiac and nervous systems have been badly damaged by a previously severe thyrotoxicosis The majority of patients with Graves disease have increased amounts of creatine in the urine which drop promptly when they are treated with iodine If the patient is given a small dose of creatine hydrate he retains less of this substance in his body than does a normal man This test developed by Richardson and Shorr is of aid in the diagnosis of atypical Graves disease, particularly when the basal metabolic rate is not elevated Salter believes that a determination of the plasma protein bound iodine gives more reliable information than the basal metabolism test in some cases The blood cholesterol level while generally lower in active Graves' disease so overlaps into the normal range that it is of doubtful value in diagnosis

The most reliable diagnostic measure is a therapeutic test with iodine The patient should be kept in bed and the basal metabolism followed for two weeks to observe the natural course of the disease Iodine is then administered and careful observations made on the pulse rate basal metabolism and clinical manifestations Patients with Graves disease almost invariably show a marked improvement Those few caught when the disease was becoming worse show under iodine a retardation in the rate of advance

Treatment—The most important part of all treatment is *physical* and *mental rest* This should if possible be obtained away from home in a place where the patient can be isolated from household cares Sometimes rest combined with small doses of iodine and a liberal diet results in a complete cure If the body weight is to be maintained it is necessary to give about twice as many calories as are needed by a normal individual under similar conditions since there is not only an increase in the resting metabolism but also an increase in the number of calories used for every muscular effort The total protein and calcium in the diet should be liberal and the vitamin allowance generous The room should be cool and quiet, and all sources of excitement must be excluded Fear of operation may raise the metabolism 50 per cent or more Sedatives such as phenobarbital are of service hydrotherapy may be tried Psychotherapy is becoming more and more important Unfortunately there are many patients who cannot afford to stay away long from their homes and *abandon the very responsibilities* that have caused the malady In such cases it is necessary either to find a more rapid method of treatment or to face the prospect of many months of invalidism

The operative treatment of exophthalmic goiter is the method of choice Patients should be observed by the physician for a period of several weeks before they are turned over to the surgeon The best results

are obtained when physicians and surgeons work together as teams Some of the severe cases are obviously unfit for any operative procedure on account of cardiac insufficiency Others are in the stage of rapidly increasing severity and an operation would precipitate a crisis Before the introduction of the use of iodine in large doses it was necessary to wait and hope that the stormy period would pass Some of these inoperable cases did well under x ray treatment Others were able to stand the short operation of the ligation of two or more thyroid arteries

Now, the use of x rays has been more or less abandoned except in special cases where operation is refused by the patient or is inadvisable for some other reason Ligations are now performed but seldom Thyroidectomy in stages may be necessary with patients who are severely ill but most surgeons try to perform subtotal thyroidectomies removing about five sixths of the gland Care must be taken to avoid injuring the recurrent laryngeal nerve and the parathyroids The operation is difficult and the mortality depends on the technic and judgment of the surgeon

The medical preparation of the patient is important H S Plummer of the Mayo Clinic in 1922 reviving an old method of treatment found that if he gave his exophthalmic goiter *patients Lugol's solution in* doses of 1 cc a day for a fortnight it caused in the large majority of cases a temporary diminution of the symptoms of thyroid intoxication and offered the surgeon a subject in comparatively good physical condition Plummer's method of treatment has been universally adopted and has reduced the mortality greatly diminishing the number of serious postoperative crises that were such frequent causes of death

Iodine in almost any form can be used instead of Lugol's solution This solution or a more palatable form such as syrup of hydriodic acid is given in divided doses well diluted with water * Patients with mild thyrotoxicosis usually receive about 15 minims (1 cc) of Lugol's solution a day severe cases three times this amount Thompson believes that much smaller doses 5 drops of Lugol's solution a day give the best results It may be given by rectum if there is vomiting In a few days there is usually a marked improvement in the symptoms and the basal metabolism falls until in a week or two it almost reaches normal The histologic picture of the glands shows a less active state, approximating that of an inactive colloid goiter or even a normal gland The remission does not last many days and it is wise not to delay the operation If the surgeon has observed his patient carefully and has used good judgment in selecting the time for operation the patient stands the subtotal thyroidectomy surprisingly well If he has delayed too long and has started to operate at a period when the basal metabolism has almost regained its previous level and the patient has shown a recurrence of symptoms, the course may be a stormy one with danger to life Therefore if the iodized patient gives evidence of a relapse it is safer to postpone operation and return to a simple treatment of mental and physical rest If the iodine is discontinued for a period of several weeks or a few months it is usually possible to obtain a second remission by giving Lugol's solution Fortunately the dreaded toxic crisis or storm is now relatively rare on account of the careful preparation of patients for operation Occasionally however patients suddenly show an increase in all symptoms and high fever Oxygen tents morphine intravenous injection of glucose hypodermoclysis and cold sponging are of help but the mortality of this complication is very high

In some mild cases of Graves' disease the patients do well on small doses of iodine (0 5–1 cc of syrup of hydriodic acid daily) over a long period of time and recover without operation We must remember always that there is a tendency toward spontaneous recovery in most cases of exophthalmic goiter The clinician in his desire to hasten recovery seldom has the opportunity of following carefully the untreated natural course of the disease One must not promise too much in the way of cure in exophthalmic goiter Patients treated with rest alone may have relapses and these are not infrequent after operation Patients who have been severely ill require a long period of careful supervision before they regain their strength The exophthalmos frequently persists cardiac damage may be permanent Myxedema

* See footnote page 1208

may result if too much thyroid tissue has been removed but this is easily controlled by the use of thyroid extract

There is still some debate as to whether or not Lugol s solution should be employed before operation in cases of adenoma with hyperthyroidism but it helps in almost as large a proportion of nodular goiters as in the diffuse toxic toxic form Patients with cardiac failure should be given digitalis but the effects are often disappointing and of course one cannot expect a slowing of the pulse rate to normal levels The important thing is to relieve the acute thyrotoxicosis by means of complete rest and iodine Operation is indicated as soon as the patient's condition permits After operation quinidine used cautiously may be of help in restoring normal rhythm in cases of fibrillation

EUGENE F DUBOIS

THYROIDITIS

Thyroiditis is a rare condition which ranges from a mild unnoticed inflammation of the thyroid to an active invasion by some pyogenic organism The tubercle bacillus seldom attacks the thyroid as a primary focus but may do so secondarily in a generalized invasion of the body Infection by other organisms may follow operative interference or may spread from some neighboring structure The symptoms are pain tenderness enlargement of the thyroid and sometimes obstruction The disease may subside spontaneously or as a result of local applications of heat or cold Operation is sometimes necessary especially if obstructive symptoms intervene Riedel has described a rare form of ligneous' or iron struma of very firm consistency

EUGENE F DUBOIS

MYXEDEMA

Definition—Myxedema is a constitutional disease occurring in adults and is due to decrease or absence of the secretion of the thyroid gland as a result of its atrophy or removal A marked decrease in the basal metabolic rate is characteristic as well as a myxedematous condition of the tissues a slowed impaired mental condition a typical facial expression and other secondary manifestations (Boothby)

History —The disease as an entity was first recognized by Gull in 18 3 and is sometimes given his name Ten years later Reverdin and also Kocher found a similar condition following total extirpation of the thyroid The latter surgeon gave it the name of *Cachexia strumipriva* Implantation of the thyroid gland was later suggested and gave temporary relief but the first permanent cure followed the administration of thyroid extract (Murray 1891) Magnus Levy discovered the low basal metabolism in 1893

Etiology—Myxedema invariably follows complete removal or destruction of the thyroid tissue either by operation thyroiditis or atrophy of the gland It occurs sporadically and in its more severe forms is rare Mild grades of the disease may be found in patients with colloid goiter and a large goiter is not incompatible with complete loss of thyroid function Myxedema occurs four or five times as often in women as in men When it develops in childhood it is called juvenile myxedema and it results in retardation of growth

Morbid Anatomy—Excluding the cases of large colloid goiter the thyroid gland in myxedema is small and atrophied Microscopically there is a marked decrease in the vesicles and a relative increase in the fibrous connective tisue The walls of the vesicles may show a round celled infiltration

Symptoms—The onset of myxedema occurs as a rule between the ages of thirty and sixty and is very gradual The symptom complex is in many ways the antithesis of that of hyperthyroidism The patients or more often the relatives notice a gradual slowing of the mental and bodily activities with an increased weight a decreased appetite and a curious change in the facial expression In well marked cases the expression is masklike the features coarse the eyelids puffy the hair of the head eyelashes and eyebrows scant The skin is dry scaly and feels thick with a curious nonpitting edema most marked in the hands feet and supraclavicular fossae The speech is thick and slow the result partly of the enlargement of the tongue and partly of the delayed mental processes and the tendency toward drowsiness As a rule the patients are placid a few are nervous and irritable Quite often they are anemic The heart is enlarged and

flabby with greatly diminished output per minute and will not stand sudden strains The joints and muscles are frequently stiff



Fig. 155—Twenty-six year-old woman with myxedema, before treatment. Basal metabolic rate —36

and painful The urine may contain albumin and the phenolsulfonphthalein test gives low results but the renal function is not significantly impaired The blood cholesterol



Fig 156.—Same patient as Fig 155 two months later after treatment with desiccated thyroid gland Basal metabolic rate —5

is high The patients may drift around for several years with a diagnosis of arthritis or obesity or nephritis before the condition is recognized and treated

If the secretion of the thyroid is entirely absent the basal metabolism falls to a level about 40 per cent below normal In milder cases the decrease in oxidation is proportional to the decrease in secretion As a result of the lowered heat production the skin is cool and the patients suffer from cold The food intake is small and there is a tendency toward gain in weight In the milder forms of the disease the patient may show few typical symptoms and in such cases a determination of the basal metabolism which will be only 15 to 25 per cent below normal often gives a clue to the loss of strength and enterprise the constipation the general ill health It must be remembered that there is a large group of persons who are not suffering from thyroid disease whose basal metabolism is also 15 to 20 per cent below the average Some of them are perfectly normal others show a low metabolism on account of chronic illness which diminishes their muscular activity and others form a vague group of neurasthenics

Treatment—The treatment of myxedema with *thyroid* is one of the brilliant achievements of modern medicine In a few weeks the patient may be almost completely restored to normal Thyroid should be given very gradually until the deficit of thyroid secretion in the body has been replaced and then administered in doses just sufficient to counterbalance its rate of destruction The various preparations of desiccated thyroid differ considerably in strength *

Dramatic effects have been obtained by the intravenous administration of thyroxin but it should never be used There is great danger in suddenly increasing the metabolism of a patient who has been living on a relatively low plane especially if the myocardium has been damaged Slower but more satisfactory results can be obtained by the oral administration of desiccated thyroid USP It is best to start with relatively small doses ½ to 1 grain a day increasing gradually until one reaches the full dose of 3 to 4 grains required in severe cases or the smaller dose that is sufficient for the milder types The symptoms disappear in the course of a few weeks and the basal metabolism rises until it is within the normal range Next comes the problem of adjusting

* See footnote page 1208

the dosage for maintenance and this must be regulated chiefly by the patient s symptoms Basal metabolism determinations are helpful It may require careful management to steer the course between hypo and hyper thyroidism Patients with myxedema should not be given morphine as its toxic effect is greatly increased in this disease

Eugene F DuBois

CRETINISM

Cretinism is a disease originating during fetal life or infancy and is due to a more or less complete lack of thyroid secretion and probably involvement of other ductless glands It is characterized by a stunted physical and mental development and a typical appearance It is not incompatible with long life

History —The disease has long been recognized It is very common in the highly goitrous districts and a sporadic type unassociated with goiter occurs rarely throughout the world The relationship to the lack of thyroid secretion was recognized by Curling in 1850 and by Fagge in 1871 In fact it was the discovery of this relationship in children which led to the recognition of myxedema in adults

Etiology —In regions of endemic goiter a lack of iodine in the mother s organism may cause a failure of thyroid development during fetal life or shortly after birth This lack produces a marked arrest in the ossification of the bones which accounts for the roentgenologic picture so highly characteristic of the disease The sporadic form probably has the same etiology as the myxedema of adults but occurring during infancy or childhood causes the characteristic dwarfing of body and mind In goiter districts there is a marked hereditary tendency and the parents may suffer from the milder forms of thyroid disease although adults with the more severe grades are usually sterile In the United States the disease is relatively rare

Pathology —There may be a complete lack of thyroid tissue (athyreosis) or the gland may be small and atrophic as in myxedema Sometimes a large colloid goiter is found

Symptoms —Talbot says that an experienced clinician may detect in the early weeks of life some thickening of the subcutaneous tissues a hoarseness of the voice and a suggestion of the facies characteristic of cretinism By the second or third month the tongue may be large and the eyes far apart with a piglike expression Usually the parents do not suspect anything wrong until the child is a year old They then begin to notice that the infant is gaining very slowly in stature intelligence, and bodily activities At this time the syndrome becomes characteristic The child is late in sitting up walking and talking Growth particularly of the extremities is stunted The skin is rough and scaly the face bloated the nostrils wide and flaring with a sunken bridge of the nose thick tongue and drooping jaw Dentition is delayed and imperfect and the teeth decay early On stripping the child one notices a pot belly and puffy pads on the buttocks and back of the shoulders Growth is very slow and the intelligence much below the normal Many cretins are unable to say more than a few words and remain uncleanly in their habits They sit quietly for hours responding to questions by a characteristic grin which wrinkles the whole face Some cretins develop a clownlike intelligence and are good humored preserving a perpetual childhood

Treatment —Prophylactic treatment is all important In goiter districts iodine must be given to pregnant women Recognition early in childhood is essential if we hope to attain a complete relief of symptoms If the arrest of development has continued for a long time it may be impossible to obtain satisfactory results Talbot recommends for infants of four to eight months ½ grain desiccated thyroid a day from twelve to twenty four months 1 to 2 grains from four to twelve years 3 to 6 grains daily When brought to normal the dose can be reduced Control of dosage by measurements of the basal metabolism is usually impossible and the treatment must be guided by clinical symptoms Thyroid preparations vary greatly in strength and in some patients they are poorly absorbed Some cretins do well on large doses but others become distinctly ill even on repeated attempts with smaller and smaller amounts With or without successful thyroid medication cretins may live to old age before they succumb to an intercurrent infection

Eugene F DuBois

MALIGNANT DISEASE OF THE THYROID

Malignant disease of the thyroid is fortunately rare in the United States, being found once in every 928 postmortem examinations It is said that a correct early diagnosis is made less frequently than in malignant tumor in any other organ The growth usually starts in a goiter or adenoma when the patient is between forty and sixty years of age About two thirds of such growths are in women

The most common form is *carcinoma simplex* The growth is firm encapsulated and on microscopic examination there is no colloid and the alveoli form closely packed columns of cells This is a most malignant form which causes metastases even though it does not penetrate its capsule *Adenocarcinomas* contain colloid and show a tendency to infiltrate *Papillary cystic carcinomas* grow slowly and are not always malignant The *scirrhous* and *squamous types* are rare *Sarcomas* may occur during the fifth and sixth decades of life

In the early stages it is difficult to distinguish between malignant growths and benign adenomas but malignancy should be suspected in any firm steadily growing tumor of the thyroid In the later stages of malignancy there may be a stony hard mass attached to the skin and deeper structures with a secondary involvement of the cervical lymph nodes or metastases into lungs skull or liver There may be pressure on the trachea or esophagus Cachexia is not striking

The occasional development of malignancy in adenomas is an argument for operation even if there are no suspicious symptoms If malignancy is suspected operation should be performed early Even then the hope of cure is small X ray and radium treatment may help inoperable cases

EUGENE F DUBOIS

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DISEASES OF THE HYPOPHYSIS (PITUITARY BODY)

THE pituitary gland and its adjacent structures in the region of the circle of Willis inspired the curiosity of Galen Andre Vesale and other early anatomists who gave it uncertain humoral properties But it aroused little interest beyond this and when comparative anatomy later made clear that structures having function in lower forms remain as functionless ones in the higher forms the pituitary (newly named the hypophysis in 1778) was relegated to the category of vestigial relics

Attention was recentered on this gland by a clinician (Pierre Marie) who in 1886 described a curious malady of hypertrophic skeletal changes in the adult which he called acromegaly It was observed some time later that there was an accompanying hypophysial tumor and assumed that this accounted for the clinical picture Moreover it was soon realized that gigantism was a related condition and differed from acromegaly merely in that it appeared earlier in life This conception of the hypophysial

relation to growth had later to be proved by further clinical observation and laborious experimentation In the process, still other functions have been ascribed to this gland until today it is recognized that growth, nutrition and reproduction, the basic functions of life have their center here

Development and Structure—The development of the hypophysis has been fairly well studied and the few remaining discrepancies are mainly those of terminology The buccal mucosa *anterior to the oral plate* develops an outpouching (Rathke's pouch) which extends upward and backward to invest a downward outpouching from the floor of the diencephalon The tubular structure of the latter is usually obliterated, leaving a *simple stalk*, the *epithelial cavity* of the buccal portion is also obliterated but occasionally remnants remain to form cysts in later life Finally the sphenoid bone unites to separate the buccal from the intracranial portions of Rathke's pouch and partly invest the gland in a bony shell known as the sella turcica A dural diaphragm penetrated by the pituitary stalk roofs the sella turcica and further serves to isolate the gland

Genetically it may be said that the development of the human hypophysis follows that common to all mammals and bears the imprint of a design which goes back to the earliest reptiles It has been surmised that such antiquity in structure must be significant of equally great constancy in function On this basis the results of experimental studies of the mammalian hypophysis may be directly applied to man

As a result of the dual origin of the gland there are two structurally and functionally distinct lobes The anterior lobe (pars glandularis) represents the derivation from the buccal mucosa and is made up of three cellular elements more properly speaking they represent a single element in two different stages of activity The chief element or mother cell possesses a nonstaining cytoplasm (chromophobe cell) which in the process of maturing acquires coarse secretory granules that stain deeply (chromophile cell) these exist in about equal proportion But the chromophile cells can be further divided into those whose granules take the acid or eosin dye (acidophile or eosinophile) and those *whose granules* take the basic dyes (basophile), they exist in a proportion of 4 1 The arrangement of these cells in cords separated by vascular and connective tissue structures conforms to glandular tissue Since there is no duct the inference is that *secretion occurs directly* into the vascular channels

The posterior lobe (pars neuralis) represents the derivation from the diencephalon and is made up of cells of glial origin plus fine myelinated nerve fibers which descend *from the diencephalon by way of the* pituitary stalk to end in a plexiform arrangement There is no glandular arrangement of cells here and scanty blood supply which is evidence enough for some that this lobe has no secretory product But others have found scattered through *the lobe* certain hyaline bodies (Herring bodies) believed to represent a secretory principle which eventually migrates into the lumen of the third ventricle The hyaline bodies may be artifacts and evidence for the existence of hormones from the posterior *lobe* is *scanty so* that this lobe biologically is still puzzling

The intermediate lobe (pars intermedia) is a structure so rudimentary in man that it appears to have no special function of its own The function and morphologic significance of the pars tuberalis are *unknown*

The blood supply to the hypophysis has a history dating back to the ancient conception of a network of vessels through which the pituitary secretion was filtered (the rete mirabile) This vascular net *following* Willis' description came to be *known* as the circle of Willis" branches from which supply a large part of the brain as well as part of the hypophysis But the intricate vascular supply to the gland both arterial and venous has more recently been formulated following comparative studies on mammals The interesting facts brought to light by this study which may have significant bearing on hypophysial function are the posterior and anterior lobes have individual arterial supplies independent of that of the *vegetative centers* in the hypothalamus the anterior lobe is drained by veins leaving its lateral border to enter *the* adjacent cavernous sinuses and no veins have been found draining either lobe via the stalk to ultimately reach the hypo*thalamic* vegetative centers

Physiology —The exact function of the hypophysis is an absorbing question to an army of both clinical and laboratory investigators and is still not entirely understood The literature on the subject to say the least is extensive and bewildering The interdependence of all the glands of internal secretion in which the hypophysis admittedly holds the dominating position plus the now well established connection between it and certain hypothalamic nerve centers has served to complicate the solution of this complex riddle The early experiments in which dwarfing obesity and sexual dystrophy resulted from hypophysectomizing puppies were later shown to be inconclusive because of the coincidental damage to structures adjacent to the pituitary body The rat, however was found to be ideally suited to hypophysectomy because the body of the gland as in the human is overlaid by a dural diaphragm and can readily be removed without damage to adjacent structures Thus in the rat an exact state of apituitarism can be produced thereby furnishing a means to test the effects of replacement therapy

If the hypophysis be removed from a young rat there results a retardation in the rat s growth and a failure to mature sexually the animal has the appearance of a delicate dwarf and is kept alive only by careful attention to diet and environment If the hypophysis be removed from a sexually mature rat there results a progressive loss of weight a degeneration of the genital system characterized by atrophy of the gonads and immediate cessation of estrus in the female as well as atrophy of other endocrine tissues including thyroid parathyroid and suprarenal cortex the animal becomes sluggish and possesses a lowered basal metabolism If the deficiency be replaced in these animals by the simple expedient of repeated intramuscular transplants of fresh hypophysial tissue from normal rats the dwarf grows and matures sexually while the adult resumes normal weight estrus returns genital atrophy disappears and the associated endocrine glands recover their former structures the general economy of both animals is greatly improved The inference then is that the changes following removal of the hypophysis are due to a lack of the secretory products of this gland Furthermore since it has been shown that these changes do not occur if the posterior lobe alone is removed it appears that the anterior lobe is entirely responsible for growth and sexual maturity

It has been possible to separate the two anterior lobe substances and to demonstrate the specific effect of each The growth hormone has been utilized experimentally to produce symmetric overgrowth of all tissues in some animals and skeletal overgrowth with hyperostosis and splanchnomegaly in others These are the counterparts of gigantism and acromegaly seen in man The sex hormone (gonadotropic hormone) introduced into young animals produces sexual precocity is undifferentiated for the two sexes and apparently acts through an intermediary effect on the gonads It has been sufficiently demonstrated that the growth promoting principle is derived from the acidophile cells of the anterior lobe and there is indirect evidence which suggests that the sex maturing principle may be associated with the basophilic elements

It would be simple enough were there but two hormones produced by the two specific types of secretory cells of the anterior lobe but it is very probable that there are several other hormones elaborated by this lobe If this is eventually found to be true it means that there are more types of secretory cells than we now know or what is more likely the product of the known types has a variable action perhaps under variable circumstances Some of the other hormones alleged to emanate from this lobe are found to influence the activity of the thyroid the adrenal cortex the parathyroid the secretion of milk and the metabolism of carbohydrates fats and probably protein The postulation of these additional hormonal properties of the hypophysis was of course foreshadowed in the first hypophysectomized animals which showed unmistakable structural changes in other endocrine glands and in distorted metabolism

Because the structure of the posterior lobe is a relatively avascular mass of glial tissue not glandular in type and its experimental extirpation fails to give convincing changes it is widely believed *to be a relatively un*important structure Pituitrin which is an

extract of the posterior lobe is not a chemically pure product, nevertheless, its effects on blood pressure, smooth muscle and urine output have been strikingly suggestive of a true hormonal property of this lobe Two fractions have been isolated from pituitrin one known as vasopressin (pitressin) increases blood pressure influences diuresis stimulates the intestine and expands the cutaneous melanophores the other known as oxytocin' (pitocin) acts solely on uterine muscles The hyaline bodies (of Herring) seen in the posterior lobe are considered by many as secretory products from the adjacent pars intermedia (derived from the buccal mucosa) and are thought to make their way into the third ventricle by way of the stalk *where they stimulate hypothalamic* nuclei of the vegetative system It has been demonstrated that cerebrospinal fluid in the third ventricle seems to have an oxytoxic and melanophore stimulating property not found in the fluid elsewhere *Furthermore when pituitrin has been in*jected into the human ventricle immediate flushing, sweating and other changes occur of striking nature and when this reaction is compared to the reverse physiologic effect of intramuscular injection it appears evi*dent that the responses result from direct* nuclear stimulation A substance resembling posterior lobe extract is claimed to have been found in the blood of patients with eclampsia and perhaps in certain patients with so called essential hypertension Also sections of the posterior lobe from a fatal case of essential hypertension show striking increase in the elements assumed by some to form hyaline bodies However these findings are to be interpreted they at least indicate that the possibility of an active posterior lobe principle *cannot safely* be ignored

Many of the functions ascribed in the past to the hypophysis alone are now found to be at least partly dependent on vegetative centers in the diencephalon Indeed it is suggested that action of the two may be reversible *impulses from the nerve centers* may influence secretion by the hypophysis and as has been suggested these secretory products may in turn stimulate the nerve centers This is not to be wondered at perhaps when it is remembered that the diencephalon is an *ancient* portion of the brain and that similar to the hypophysis it has remained essentially unaltered through phylogenetic development The anatomic juxtaposition of the two and the direct neural connection imply that they are inseparable and important to perpetuation of the species Obviously disease involving one may likely involve the other Water balance fat metabolism and carbohydrate metabolism are the principal processes concerned in this implied mechanism while heat regulation and *pathologic sleep are additional features* of any disease that involves the diencephalon as well as the hypophysis

The interrelationship of the different hormonal glands must also be given due consideration Much of what was originally *thought to be the result of direct influence* of hypophysial secretion is now known to result from secretions of other glands activated by the hypophysis The gonad stimulating hormone has been found to have a dual effect on the ovary namely stimulation *of normal follicular growth and ovulation* (folliculizing hormone) and the formation of premature corpora lutea (luteinizing hormone) These changes in the ovary are responsible for the menstrual cycle and this cycle ceases if either the ovaries or the *hypophysis are removed A comparable* relation exists with the thyroid in which it has been shown that ablation of the hypophysis produces states of hypothyroidism Similar relationship prevails with the suprarenal cortex the parathyroids and possibly the *pancreas—thus* the terms gonadotropic thyrotropic' corticotropic parathyrotropic and pancreatropic' hormones There are also instances of reciprocal action as for example the marked alterations in the hypophysis caused by *ovarian secretion* during pregnancy In addition whereas some hormonal interchange is blood borne there appear to be instances in which we may assume that the hypophyseal secretion exerts its influence on other glands of the body through its action on the vegetative centers innervating that gland

One more variable recently come to light is the antihormone theory prompted by the observation that in prolonged treatment with certain pituitary extracts there is a progressive diminution in effects This is

ascribed to the formation of antihormones and suggests that such a process may be responsible in certain cases for hypoglandular states The hypothesis is attractive yet not well justified on the basis of present information

An appreciation of these complicated functions of the hypophysis is necessary before attempting to understand the various clinical manifestations resulting from pathology in and about the gland

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CLINICAL CORRELATION—THE COMMON TYPES OF PITUITARY DYSFUNCTION

To attempt to transfer what knowledge the laboratory provides to clinical experience is a difficult and perplexing task Processes in the human body are not in all respects exactly comparable to those that can be produced in the experimental animal This is partly due to the ability of the human body to adapt itself to pathologic processes even to the degree of masking such effects as might otherwise be expected In addition experimental work has been largely limited to removing the activity of the hypophysis no activation of the gland itself has yet been produced comparable to nature s experiment in man

Conflicting observations of clinical cases must await explanation until the eventual marshalling of incontrovertible facts and no doubt much of what we now believe will be greatly modified in the course of time

However for practical purposes from the admittedly incomplete evidence at hand the clinical manifestations of hypophysial disease are divided into hypo and hyper pituitarism For those syndromes in which it seems impossible to decide which of the pituitary states exists some have resorted to a third division heteropituitarism or dys pituitarism

The hypopituitary state results either from idiopathic undersecretion or from destruction or compression of the hypophysis Complete or partial destruction may follow trauma such as skull fracture in the region of the sella turcica or degeneration may follow inflammatory or vascular disease of the hypophysis The acute infections of childhood upper respiratory infections, typhoid fever and syphilis are possibly causative factors in some instances Compression of the gland results from expanding adenomas gumma metastatic carcinoma and from other tumors that arise outside the gland but in its immediate neighborhood

Dwarfism.—The lack of hypophysial secretion in infancy or childhood results in varying degrees of underdevelopment Individuals thus affected range from just under the lower limits of normal to frank dwarfing Such dwarfs may be normal at birth and thereafter until delay or complete cessation of growth occurs or they may be already too small when born (primordial dwarfs) and develop at a delayed rate But the term dwarfism requires qualification for in a broad sense it includes all conditions characterized by stunted growth Thus the etiologic possibilities are numerous and varied and often there is lack of agreement concerning the category into which a given case should be placed The term infantilism commonly used synonymously with dwarfism strictly applies to individuals in whom there is impairment of growth sex and intellect while the term nanism is used to imply conditions in which there is impairment of growth only In the type of arrested development due to secretory deficiency of the hypophysis the mentality is rarely retarded though in the majority of instances there is lack of sexual development and regarding the things that are influenced by sex it perhaps may be said they do not become mentally mature

Hypophysial dwarfs are usually children of normal parents though it has been reported that occasionally there have been ancestors with various forms of hypophysial disease In hypophysial dwarfism there is good symmetry of the body and the physical make up is essentially that of early childhood in which the lower measurements are relatively short Obesity is not a feature of the pure form of this condition and most individuals are thin During the age of childhood these individuals simply appear to be small for their age but later they develop a mature appearance and as time passes a frankly oldish and even wizened look develops which is incongruous with their infantile stature (progeria) The genitalia re-

main in an underdeveloped state also but in proportion to the general physical development are not small The secondary sex characteristics are absent or retarded and usually there is amenorrhea in the females and aspermia in the males There are records nevertheless of hypophysial dwarfs producing normal offspring There is no gross evidence of dystrophy of bones or joints but the skeletal framework is smaller and more fragile than normal and epiphyses remain open much longer The appetite is small and an attempt to increase the caloric intake is usually futile There is sometimes an increased tolerance for glucose otherwise the blood chemistry is normal The basal metabolism is usually low but within the range of normal unless there is an associated hypothyroidism of some degree There is no change in the water balance and no characteristic change in the urine

Occasionally roentgenograms of the skull have shown a proportionately small or a completely bridged sella turcica but this is not a common finding in hypophysial dwarfism and the size of the sella cannot be used as an index of function of the gland A craniopharyngioma or even an hypophysial adenoma may be the cause of dwarfing and the sella in these cases may be considerably enlarged In the final analysis however the exact diagnosis depends largely on the operative or postmortem demonstration of an abnormal hypophysis and in instances in which the elements of the anterior lobe are found simply to be deficient the etiologic factors can only be speculated upon

In the differential diagnosis of hypophysial dwarfism every other cause of arrested development must be eliminated Considering all the possibilities of abnormal germ plasm the effects of systemic diseases and of abnormal diet and the interrelationship of all the endocrine glands it is doubtful whether any type of dwarfism can be said to have an uncomplicated etiology Dwarfing which is not directly the result of hypopituitarism may be disproportionate or proportionate The former appears in certain diseases of the bone in which limbs or trunk are misshaped or are out of proportion with each other as occurs for example in achondroplasia rickets Pott's disease of the spine and osteopsathyrosis The latter is seen as a result of chronic infections intoxications or nutritional deficiencies that exist during the growth period among these diseases may be mentioned tuberculosis syphilis cardiovascular disorders, and digestive disorders such as pancreatic insufficiencies and celiac disease The dwarfing of cretinism is an example of underdevelopment resulting from disease primarily involving the thyroid but it is likely that in this disease associated hypophysial dysfunction is partly responsible for growth and other deficiencies The same may be said for dwarfing seen in diseases of other endocrine glands The condition sometimes referred to as ateliosis is so akin to what has just been described as hypophysial dwarfism that the two may be considered one and the same

Dystrophia Adiposogenitalis of Frohlich—The most common cases of hypopituitarism by far are the adolescent boys and girls who become obese and show delayed puberty the stature may be small but this is inconstant The boys have a slightly feminine type of body with degrees of obesity about the thighs buttocks breasts and face The fat has a hard firm feel The genitalia are small and often the testicles descend imperfectly or not at all The axillary and pubic hair is scant and of fine texture the beard thin or absent The girls have similarly distributed obesity and the breasts which enlarge moderately with fatty tissue contain no glandular substance The pubic hair is sparse and the external genitalia small The uterus is similarly infantile menses begin late and are variously abnormal These youths may be mentally bright, even precocious but often are listless and sluggish failing to concentrate long on any protracted task The muscular system has an abnormally low tonus frequently associated with hyperextensibility of the joints Basal metabolism is normal or lowered and the sugar tolerance tends to be increased

The classic cases of this description are associated with craniopharyngiomas which compress the hypophysis But obviously all the children that appear with this condition do not have such tumors what pathologic changes are present in the hypophysis is not always known

A typical state of hypopituitarism seen in the adult is that accompanying chromo

phobe adenomas of the hypophysis, and described under that heading Cessation of menstruation is the usual occurrence in the women but hypopituitarism is not always expressed as amenorrhea It appears that the condition of hypertrophic endometritis excessive bleeding and dysmenorrhea may be the result of a deficiency in the gonadotropic hormone more particularly the luteinizing fraction

Simmonds Disease —An extreme example of hypopituitarism is an insidious condition that occurs usually during maturity It is the result of extensive degeneration of the hypophysis from one cause or another and characterized by cachexia of remarkable degree wasting is so marked that the patient is literally ' skin and bones There is precocious senescence manifest by loss of hair falling out of teeth and dry wrinkled toneless skin Pulse blood pressure and temperature are all subnormal basal metabolism is reduced and there may be hypoglycemic crises There is no sensation of hunger or thirst and the excretion of water is reduced perhaps impaired These patients become depressed, finally comatose and death follows Although there are authentic cases of this condition with atrophy of the hypophysis a word of caution is in order for cases with the same or similar clinical picture appear without pituitary atrophy and may recover on merely being forced to eat and drink

Diabetes insipidus a state of polyuria and polydipsia hardly needs be mentioned as a manifestation of hypopituitary function in the light of present knowledge for it now appears to be the result of hypothalamic lesions However it frequently accompanies hypopituitary states and the effect of pituitrin on the condition is well known

Hyperpituitarism at least one type of it produces individuals of inordinate height Gigantism and acromegaly are both manifestations of eosinophile adenomas of the hypophysis though presumably there are periods of overgrowth at various times of life resulting from hypereosinophilism not associated with adenoma formation Basophilism is possibly another form of hyperpituitarism both are discussed with the adenomas

The adenomas of the hypophysis as a whole together with the craniopharyngiomas represent the largest group of cases about which we have a fairly definite knowledge concerning the clinical and pathologic changes that go with hypophysial disease These will be discussed as a group

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HYPOPHYSIAL ADENOMAS

Adenomas are prone to occur rather commonly in the hypophysis though actually they exist in a small percentage of the cases usually thought to demonstrate clinical evidence of hypophysial disease They produce in every instance a striking group of symptoms which have been considered as manifestations of hypo or hyperpituitarism or occasionally a mixture of both The extensive clinical study of these cases has played almost as great a part as has laboratory experimentation in establishing the function of the hypophysis The tumors always arise in the anterior lobe none are known to exist in the posterior lobe They occur primarily in young adults about equally in the two sexes and vary in size from a few millimeters to 5 to 6 cm in diameter

Corresponding to the three types of cells in the anterior lobe there are three different types of adenoma chromophobe eosinophile and basophile The chromophobe and chromophile adenomas occur in a ratio of about 3 1 the basophile are extremely rare and never attain an appreciable size The chromophobe adenomas are usually larger than the eosinophile but otherwise both have as a rule a soft friable and vascular gross appearance

Histologically the chromophobe adenoma is composed of cells arranged in strands or groups separated by a stroma of connective tissue and blood sinuses The delicately granular cytoplasm stains faintly and the nuclei are large in rare instances there may be mitotic figures In the eosinophile adenoma the cells form loose clusters without stroma and with fewer blood vessels The granules of the cytoplasm stain with eosin and the nuclei also large show no mitotic figures Between these two transitional

types occur which are known as mixed adenomas but they are predominantly chromophobe adenomas with eosinophile elements The cells of the small basophile adenomas possess granules staining with the basic dyes and many of them are multinuclear It might be expected that these tumors being epithelial in origin might become carcinomatous but rarely does one find more than occasional mitosis and in general the tumors are comparatively slow growing

As the adenoma grows it displaces and compresses the rest of the hypophysis until the gland may be hardly recognizable The dural envelope of the hypophysis and the bony confines of the sella turcica are more resistant but they too finally yield The sella turcica gradually increases in size (normal dimensions—10–14 mm anteroposterior by 14–15 mm in width by 8 mm deep) usually symmetrically giving it a characteristic ballooned appearance clearly discernible in the x ray plate Eventually the dural diaphragm covering the sella turcica or the thin floor separating it from the sphenoid sinus will give way Usually the floor does not completely disintegrate but when it does the tumor invades the underlying sinus and may even appear as a projection in the nasopharynx If the dural diaphragm above ruptures as it frequently does the enlarging tumor pushes the optic chiasm upward and backward at the same time flattening and stretching the optic nerves

As a result of encroachment on the chiasm the decussating optic fibers are physiologically interrupted or become degenerated thus producing atrophic changes in the nerve head and changes in the visual fields which at first are characteristically bitemporal upper quadrantal defects With progression of the growth the bitemporal defect becomes complete and implication of the macular fibers impairs the capacity for reading ordinary print Eventually the optic nerves degenerate resulting in total blindness Infrequently the tumor may project posterior to the chiasm and though the dominant changes in the visual fields are still bitemporal the early defects are less likely to be manifest in the upper quadrants Should such a posterior projecting tumor grow laterally, the optic tract on that side might be compressed producing a contralateral homonymous hemianopia

Once the tumor has broken through the dural diaphragm it takes on the aspects of any other intracranial tumor Though these growths rarely attain massive size, encroachment on the floor of the third ventricle producing hypothalamic symptoms, does occur and occasionally further extension in this direction blocks the ventricular system producing internal hydrocephalus with its accompanying symptoms The form of the growth is usually globular and tends to lie in the midline but occasionally it may spread irregularly to encircle the carotid arteries it may compress the oculomotor nerves producing extra ocular palsies it may invade the temporal lobe producing uncinate seizures and other temporal lobe symptoms, cases have been reported even of extension through the tentorial incisura into the posterior fossa

Degeneration or hemorrhage in these tumors is not uncommon and results in cystic formations These degenerative processes account no doubt for the unexpected remissions of symptoms observed in some cases

Each of the three varieties of hypophysial adenoma has been found to have distinctive constitutional manifestations wholly apart from the local pressure effects on the intracranial structures (producing so-called neighborhood signs) The chromophobe adenoma whose cells are thought to have no hormonal function produces a train of symptoms which have been considered to represent a state of hypopituitarism resulting from compression of the hypophysis The eosinophile adenoma whose cells are believed to have a growth producing function are always associated with signs of overgrowth—gigantism or acromegaly—and the intensity of the overgrowth varies with the degree of eosinophilia The basophile adenoma whose cells by deductive reasoning are thought to have gonadotropic function are now believed to produce an equally striking clinical syndrome The proportion in a series (by Cushing) of 385 verified cases of hypophysial adenoma was 277 chromophobe 107 acidophile and mixed and 1 basophile Each of these will be taken up separately

Chromophobe Adenoma (*Hypopituitarism*) —By far the most common tumor of

the hypophysis is the chromophobe adenoma In view of the fact that to other adenomas of the hypophysis and indeed, to those of most ductless glands a hypersecretory function is ascribed one would expect the chromophobe adenoma to possess similar properties On the contrary it is an exception to the rule for chromophobe cells are known to be functionless Yet by the mechanical compression of the remainder of the hypophysis the adenoma produces a the face and neck The hands appear pudgy and the fingers delicate and tapering the nails showing no crescents The hair is scant and of fine texture, in males the beard requires infrequent shaving and the pubic hair takes on a female distribution A moderate adiposity develops of feminine distribution or more nearly like the indifferent infantile contour Menstruation ceases in the female and impotence and loss of libido occur in the male The temperature is frequently sub



Fig 157.—Roentgenogram showing destruction of posterior clinoids and floor of sella turcica caused by chromophobe adenoma of pituitary

state of hypopituitarism with symptoms less dramatic but just as recognizable as those resulting from hyperpituitarism

The sexes are equally affected and the incidence of the disease is about evenly distributed in the three decades between twenty and fifty In isolated cases the disease has appeared after fifty and in a few before twenty Should the child or adolescent be afflicted he becomes dwarfed and fails to mature sexually This clinical picture is more frequently encountered in other conditions of hypopituitarism the most usual being the craniopharyngioma

Hypopituitarism in the adult produces symptoms of sluggishness lassitude fatigue and an unusual sensitivity to cold The complexion becomes pallid and the skin dry thin and delicately wrinkled especially over normal the pulse slow and the basal metabolism materially lowered

Although the chromophobe adenoma has a tendency to grow to a larger size than the eosinophile adenoma the resulting symptoms and signs never take on the aspect of profound hypopituitarism manifest by the advanced cachexia and senility of Simmonds disease in which the last vestige of the hypophysis is destroyed

Headache of frontal and temporal distribution commonly accompanies an expanding hypophysial adenoma though the exact mechanism by which the headache is produced is not established The sella turcica balloons as the adenoma enlarges and when the growth finally breaks out of its confines as it does in a very large percentage in this type of adenoma the neighborhood signs

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notices an increase in dimensions and shape of his hands and feet X rays show a proliferation at the tips of the distal phalanges spoken of as tufting The palms and fingers become broadened producing a square spadelike appearance of the hand The entire hand looks puffy though creased, and feels stiff to the patient He is made aware of these changes further by the necessity for increasing both his glove and shoe size At the same time the facial features coarsen the lips thicken the nose takes on an overgrown bulbous appearance and the nostrils widen The head becomes large and supraorbital ridges prominent from thickening of the skull bones Similar overgrowth of the mandible produces a square protruding jaw (prognathism) and widely spaced teeth The jaws frequently match so badly that mastication is impaired The tongue becomes so large and awkward as to impede lingual speech The skin everywhere hypertrophies and wrinkles and the scalp particularly is loose and ridged like a bulldog s Perspiration is profuse and possesses a peculiar acrid odor noticeable to the patient as well as to others Hypertrichosis is usual and when superimposed on the prominent supraorbital ridges gives a striking beetle-browed appearance There is a stoop to the shoulders and the general appearance takes on the aspect of a ferocious caricature almost frightening until one hears the lisping (though deep voiced) speech and sees these weakened miserable creatures break into tears as they so frequently do

Later on the patient experiences dull headaches in the frontal or bitemporal regions from distention of the dural envelope of the hypophysis He feels extreme weakness and lassitude and becomes easily dyspneic on exertion He is uncomfortable with backache with neuralgic pains and paresthesias in the extremities He is constantly hungry and may have increased thirst and polyuria The basal metabolism at this time will show an increase and a glycosuria is present which is notably resistant to insulin therapy Menses in the female and sexual libido and potentia in the male are sometimes increased in the early stages but eventually diminish or disappear entirely

With the enlargement of the adenoma the sella turcica balloons giving the characteristic picture on the x ray plate in about 90 per cent of the cases A third of these never reach sufficient size to break out of the natural confines The others extend into the intracranial cavity and present the usual signs of chiasmal hypothalamic or temporal lobe compression

The progress of the disease is usually self limiting Occasionally it appears to have remissions and exacerbations and there are cases which show only slight acromegalic features (fugitive acromegaly) In the course of most acromegalics a phase of hypopituitarism appears The skin softens, hair falls out the disagreeable perspiration ceases polyphagia polydipsia and polyuria subside feebleness increases basal metabolic rate becomes normal or subnormal, and diabetes mellitus if present may disappear



Fig 159 —Roentgenogram of skull of an acromegalic with verified eosinophile adenoma of the hypophysis Note the ballooned sella turcica, thick skull large frontal sinus and large mandible

If there is progression death may result from intracranial extension or from cardiovascular complications associated with the hypertrophic changes that affect the heart and blood vessels But even progressive cases may go on for many years one is recorded as having a fifty year duration and a patient who lived to be eighty three had symptoms for thirty eight years the tumor having become cystic

resulting from compression of the optic chiasm, hypothalamus, temporal lobe and others appear

The differential diagnosis is usually not difficult The enlarged sella turcica points to an adenoma (except in those rare instances of gumma or metastatic carcinoma of the hypophysis) and certainly there should be no difficulty in distinguishing the appearance of hypopituitarism of the chromophobe adenoma from the acromegaly or gigantism of the eosinophile adenoma The lesions about the sella turcica producing hypopituitary symptoms do not characteristically balloon the sella though the hypophysis is compressed and the clinoid processes may show destruction A disconcerting occurrence, as far as early and accurate diagnosis is concerned is the occasional rupture of the chromophobe adenoma through the diaphragma sellae without previous erosion of the sella turcica But the gravest danger is in not diagnosing a tumor at all until the patient s vision has undergone perhaps irreparable damage

Eosinophile Adenoma (*Hyperpituitarism —Gigantism and Acromegaly*) —The classic description of two cases of this remarkable disease by Marie in 1886 laid a foundation for all subsequent clinical studies The acral enlargements, on which the clinical recognition of the disease rests served to name the disorder The final proof of the part played by the eosinophile adenoma of the hypophysis came a number of years later

The disease occurs in adults and appears most commonly between the ages of twenty and thirty though rare cases have been thought to begin as late as fifty If it begins before twenty that is, before the epiphyseal lines have closed the clinical picture is that of gigantism, almost all circus giants are examples of this Acromegalic features may never appear if the hypophysial adenoma becomes inactive before maturity but if it continues to be active acromegalic features superimpose those of gigantism and all transitions between the two may result It is far from being a disorder which affects all its victims in the same way or in equal degree The disease is not hereditary but occasionally is familial It occurs about equally in male and female and in the latter may follow soon after pregnancy

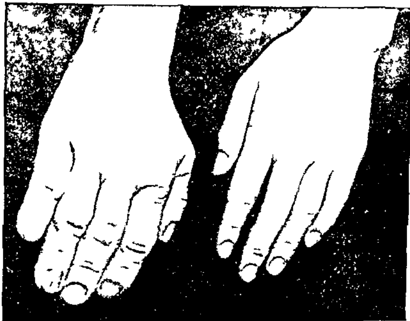


Fig 158 —Hand of a woman with acromegaly compared with normal woman s hand

Whereas in gigantism there is a general ized symmetric increase in size particularly in the length of bony structures in acromegaly there is a localized increase in the size of various structures producing a curious bodily configuration which cannot be mistaken for any other malady The changes occur slowly but eventually the patient

symptoms is in proportion to the amount of tumor removed But the pituitary insufficiency which may result from too radical removal may be much more disagreeable than the acromegaly and it is to be remembered that operation is performed only for the purpose of saving vision and relieving the symptoms of extrasellar extension

Following successful operation there are all degrees of improvement Reestablishment of normal menstrual cycle is frequent and pregnancy is possible potentia and sexual libido may return in the male There is usually great improvement in the appearance and well being of the patient Though there is little hope for the restoration of vision once blindness has supervened many of those patients with partial loss get complete return of visual function and others regain a part of it

Basophile Adenoma (*Pituitary Basophilism—Cushing Syndrome*) —A curious clinical syndrome was pointed out by Cushing (*in 1932*) which he termed pituitary basophilism" and ascribed to the presence of an hypophysial adenoma made up of basophile cells

It will be recalled that there appear to be at least two established functions of anterior lobe secretion—growth provoking and sex maturing And there are three kinds of cells in the anterior lobe chromophobe eosinophile and basophile, each known to develop adenoma forms The cells of the chromophobe adenoma are functionless whereas the cells of the eosinophile adenoma have been shown both clinically and experimentally to promote growth By inference therefore the basophile cells and the sex maturing hormone represent a combination of cause and effect it merely remained to be found which one of the many clinical dyspituitary states was the resulting syndrome of the basophile adenoma This in



A B

Fig 161.—*Girl fifteen years of age, with basophilism (one of Dr Cushing's original cases) A Note the plethoric appearance of the face with abnormal growth of hair on brows and face B Note the obesity of the trunk and round shoulderedness also the abdominal striae (Courtesy of the Archives of Surgery)*

Besides the overgrowth of subcutaneous tissue and bone manifested by the external appearance of the acromegalic patient post mortem examination reveals widespread splanchnomegaly of unusual degree involving all organs of the thorax and abdomen There is an evident tendency for the other ductless glands to develop hypertrophic and adenomatous changes sometimes with associated alterations in their function

Treatment of the Chromophobe and Eosinophile Adenoma—So far there is no outstanding therapy with which to supplement hypopituitarism and there is none to counteract hyperpituitarism except x ray radiation and surgery The use of x ray therapy to reduce the growth of the chromophobe adenoma has on the whole been disappointing although the beneficial results in the occasional case make a therapeutic trial worthwhile Unlike the chromophobe adenoma the eosinophile adenoma is relatively sensitive to x ray therapy and unless the tumor has extended outside the sella turcica producing neighborhood signs operation is to be avoided If there is no immediate danger to vision therefore x ray therapy should always be tried for it may retard or even stop the growth This is not entirely without danger however, for edema or hemorrhage may result in a degree sufficient to produce blindness or more serious symptoms if the tumor has a tendency to invade the cranial cavity It is now common practice in the majority of cases in which part of the adenoma has been surgically removed to follow with a complete series of x ray treatments

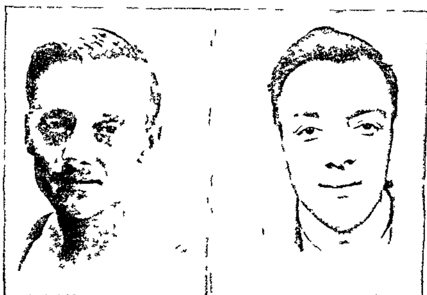


Fig 160—Photographs of the same patient taken ten years apart The one on the right shows the development of acromegaly during the interval

Surgery on these patients offers numerous hazards but must not be delayed when indicated that is when the tumor has extended beyond the sella turcica These patients are notoriously bad surgical risks and experience shows that the reserves upon which one depends in grave surgical procedures are unaccountably lacking The choice of operative approach to the tumor hardly offers a problem except to the surgeon Formerly a transsphenoidal approach to the sella turcica was used but obviously extrasellar extensions of the tumor are impossible to reach with this approach and meningitis is a hazard The various intracranial approaches allow better exposure although with the necessary retraction of the brain the hypothalamus may be damaged and postoperative extradural blood clots and cerebral edema are prone to form

It is also difficult to decide how much of the tumor to remove There is always a tendency to do a more radical extirpation than is safe in an attempt to prevent a recurrence In the acromegalic especially the improvement in the hyperpituitary signs and

symptoms is in proportion to the amount of t mor removed But the pituitary insuf ficiency which may result from too radical removal, may be much more disagreeable than the acromegaly and it is to be remem bered that operation is performed only for the purpose of saving vision and relieving the symptoms of extrasellar extension

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brief, was the reasoning behind the prediction of a basophile adenoma in an obese and hirsute young woman of twenty who began at nine to have profuse menstrual flow At fourteen she had attained adolescence and menses became most irregular At fifteen she had grown exceedingly obese eventually reaching 206 pounds She died of an intercurrent infection and, on postmortem examination was found to have a small hypophysial adenoma made up of basophile cells

In his original paper dealing with this subject Cushing collected a group of twelve patients all young adults from which the following features were characteristic of all cases (1) a rapidly acquired and usually painful adiposity confined to face neck and trunk (2) a tendency to kyphosis from a peculiar softening of the bones of the spine, (3) sexual dystrophy shown by early amenorrhea in the females and ultimate impotence in the males (4) an alteration in normal hirsuties shown by hypertrichosis of face and trunk in all females as well as preadolescent males and possibly the reverse in the adult males (5) a dusky or plethoric appearance of the skin with purplish striae (6) vascular hypertension (blood pressure varying from 230/170 to 178/100) (7) a tendency to polycythemia (8) variable backaches abdominal pains fatigability and ultimate extreme weakness A list of other less constant features includes acrocyanosis ecchymoses aching pains in the eyes slight exophthalmos dryness of skin polyphagia polydipsia, polyuria edema of the lower extremities and an unusual susceptibility to infection

While Cushing s syndrome is more often found to be associated with basophilic adenoma with or without adenomas of the adrenals there are a number of authentic cases in which the syndrome is accompanied not by an hypophysial adenoma but by a malignant tumor of the adrenal In a few cases autopsy has failed to reveal tumors of either the hypophysis or adrenal But in all cases it is believed that there exists in the basophilic cells of the hypophysis certain degenerative changes described by Crooke

In any case the evidence such as it is suggests that the syndrome is in the nature of an hyperadrenocorticism whether the state is initiated in the hypophysis or the adrenal and the clinical features are sufficiently constant to establish the syndrome as a disease entity

Treatment —None of the basophile adenomas reach sufficient size to produce pressure changes and therefore do not require surgery It would be expected however that these adenomas like the eosinophile, would react favorably to x ray radiation and this to a degree has been found true In cases where there is sufficient reason to suspect the presence of an adrenal cortex tumor operation on this gland should not be withheld

Albright and his associates have stressed that in this syndrome there predominates an overproduction of sugar with decreased glucose tolerance and a decreased availability of amino acids with which to build protein The administration of testosterone proprionate has had some beneficial effects

BRONSON S RAY
GEORGE J HEUER

CRANIOPHARYNGIOMA

After Marie s description of acromegaly and later after its probable association with tumor of the hypophysis had become known reports began to appear of instances of hypophysial tumor without acromegaly Most of these cases presented a picture of hypopituitarism and Frohlich (in 1901) described in detail a case of an obese boy with underdevelopment of the genitalia Since then it has been found that the clinical picture is often the result of a cystic tumor arising from epithelial rests due to an imperfect closure of the craniopharyngeal duct This duct it will be remembered is a part of the outpouching from the buccal mucosa which unites with an outpouching from the diencephalon to form the hypophysis

Craniopharyngioma is the usual name given this tumor though it is variously called suprasellar cyst hypophysial duct tumor craniopharyngeal duct tumor Rathke s pouch tumor and on a histopathologic basis 'adamantinoma epithelioma etc The size may vary from a few millimeters giving no symptoms to one

of unusual proportions, giving many symptoms Occasionally these tumors are solid but usually they are cystic with a comparatively tough though thin wall in which is found the cauliflower-like epithelial tumor mass in various stages of degeneration and calcification The cyst also contains varying amounts of viscid, yellow brown fluid which when held up to the light has the iridescent appearance of machine oil and on closer inspection, is seen to contain shimmering crystals of cholesterin which testify to its epithelial origin

Since these are congenital tumors symptoms may arise from them at any time in life What influences the growth of these embryonal rests is unknown of course but with surprising frequency there is a history of preceding and possibly associated trauma About half of the cases develop symptoms during childhood and adolescence, the rate of frequency steadily diminishes after twenty and only rarely will a case appear with symptoms beginning after sixty The sexes are affected equally These tumors are not rarities but (in Cushing s series) comprise 4 per cent of all verified intracranial tumors and are about half as frequent as the chromophobe adenomas from which they must be differentiated clinically

The tumors may arise above or below the diaphragma sellae Those arising below it may do nothing more than compress the hypophysis or they may grow upward and involve structures about the sella just as the hypophysial adenomas Those arising above the diaphragm involve the optic chiasm and other parasellar structures early but they too usually compress the hypophysis In doing so they cause erosion of the clinoid processes and dorsum sellae and produce changes different from the symmetrically ballooned sella caused by the hypophysial adenoma On the whole these tumors tend to grow larger than the adenomas and a not infallible rule is that the earlier in life they make their appearance the larger they are likely to become Though they tend to grow upward in the midline some project in other directions and it is not unheard of for one of them to grow through the tentorial incisura into the posterior fossa giving as first symptoms those of a cerebellopontine angle tumor

The symptoms show a wide variation, as would be expected on considering the gross features of the tumor Compression of the hypophysis produces a state of hypopituitarism damage to the optic chiasm impairs vision invasion of the hypothalamus disturbs the center of the vegetative nervous system and blocking of the third ventricle results in internal hydrocephalus In addition the manifestations of these states and



Fig 162—Two children of the same age The one on the right is normal The one on the left developed a craniopharyngioma at the age of five Note the complete cessation of growth

the complaints differ greatly depending on the time of life in which they appear Children complain most of headache and vomiting adolescents and young adults of sexual changes and personal appearance and older adults of failing vision

The children afflicted with this tumor present a striking appearance of underdevelopment This may take the form of general dwarfing with normal proportions or there may be a tendency to obesity or still another

group may show emaciation—known as the Loraın type ' The tardy growth or delicate appearance is frequently disregarded by parents as is the usual enuresis of these children But eventually the increasing headache and vomiting bring them to the physician who finds evidences of hydrocephalus in the enlarged head, separation of cranial sutures choked disks and sixth nerve palsy In the early stages, the children are notably bright and even precocious but sluggishness and somnolence supervene with advance of the disease In the very late stages there may be fits of violent thrashing about, retraction of the head and extensor spasms of the extremities Lowered metabolism and subnormal temperature are expected but a hyperthermia is likely to accompany the final events

Children who pass into adolescence with pituitary insufficiency undergo no sexual development, the girls do not menstruate and the boys are apt to have underdeveloped genitalia If the disease begins during adolescence or young adulthood menstruation stops in the female and sexual libido disappears in the male The body becomes moderately obese and in both sexes takes on the asexual contour of a child Growth stops or is slowed up giving the appearance of being younger than the actual age This is frequently spoken of as infantilism though the term should not imply mental retardation for these individuals are often mentally bright—even brilliant and are characteristically pleasant and likable The skin is delicate and pallid in some there is fine wrinkling of the skin about the face and neck which together with the small size suggests early senescence—a condition known as progeria There is scanty fine hair over the body and in the male female distribution at the pubis and lack of beard Frontal and bitemporal headaches develop and vision begins to fail

Older patients are less apt to show changes in bodily configuration but the hair becomes scanty and the skin wrinkled Menses and libido disappear indeed their disappearance may long precede the later symptoms of headache and failing vision Lassitude and somnolence are common Basal metabolism and blood pressure tend to be lowered

The *failing vision* in any of these patients is usually due to pressure on the optic chiasm the optic nerves in front of it, or the optic tracts behind and just as in the hypophysial adenomas the tumor may displace the chiasm forward or backward The characteristic visual defects are at first in the temporal fields but the configuration of the blind areas tends to be bizarre and less regular than is seen in cases of hypophysial adenoma The flat pallor of primary atrophy is seen in the nerve heads and complete blindness may finally result In some cases the chiasm may be largely spared but, if hydrocephalus develops, papilledema and secondary optic atrophy follow also producing failing vision One may expect sometimes, to find a combination of both of these processes Diplopia may be present as a result of direct compression of the third fourth or sixth nerve or a sixth nerve palsy may accompany the increased intracranial pressure of hydrocephalus

The mechanism of the internal hydrocephalus can be clearly understood by picturing the tumor obliterating the third ventricle and blocking the foramina of Monro The lateral ventricles dilate and headache vomiting and papilledema follow This headache is more severe and generalized than the frontal and temporal headaches that often accompany less extensive tumors in the region of the sella

There remains (for brief consideration) a group of interesting phenomena often and particularly associated with craniopharyngioma which are the result of damage to the hypothalamus This region contains the central nuclei for the entire vegetative nervous system its complicated blood supply from the circle of Willis and its connection with the hypophysis through the hypophysial stalk are frequently destroyed or injured by the tumor Lesions of the hypothalamus produce most notably states of pathologic sleep cardiac irregularities hyperthermia maniacal attacks inequality of pupils adiposity and diabetes insipidus The last two adiposity and diabetes insipidus are particularly interesting because of the dispute over the part the hypophysis plays in their production Without answering the question raised it may be said that both states may result from emboli or infectious processes

involving only the hypothalamic centers Also it may be said that the classic state of dystrophia adiposogenitalis Frohlich s syndrome does not result from hypopituitarism alone but from a combination with injury to the hypothalamus

The ataxic phenomena spastic states with retraction of the head and extension of the extremities seen in advanced cases, are due to compression of the *descending motor* tracts

The differential diagnosis for the most part is made from hypophysial adenomas and rarely from a few parasellar tumors The clinical pictures of the states of hyperpituitarism resulting from the chromophile adenomas offer no difficulty The hypopituitary syndrome of the chromophobe adenoma *is the one most likely to be confusing* There are several distinguishing features however *i.e.* the age limits are of some aid since adenomas never appear before fifteen but most of the craniopharyngiomas appear before that the sella turcica in the case of the craniopharyngioma shows on the x ray plate *irregular erosion mostly involving the* clinoid processes and the dorsum sellae unlike the ballooning of the sella from adenoma 80 per cent of the craniopharyngiomas show calcified areas in the tumor on the x ray plate the visual field defects of the adenoma are more regular

If there is any question with regard to the cause of hydrocephalus ventriculography is invaluable

Other lesions which may exist in the region of the sella turcica and optic chiasm are gliomas of the chiasm meningiomas arising from the tuberculum sellae tumors arising *from the floor of the third ventricle* rare tumors such as chordomas and cholesteatomas and chronic circumscribed arachnoiditis which may simulate tumor There are features in each of these that facilitate differential diagnosis but even though diagnosis is uncertain whenever vision is impaired operation is indicated

Treatment of Craniopharyngioma — Surgery is the only logical treatment for craniopharyngioma But to remove the entire growth without destroying or damaging the *surrounding structures is difficult* and usually the surgeon must be content with something less radical Merely tapping the *cyst will frequently serve to give long pe*riods of remission and some few may have no recurrence but at least a partial removal of the cyst wall is desirable If the cyst refills a succession of taps may serve to carry the patient along quite well but there is an unfortunate tendency for this type of refilling cyst to become progressively solid In such cases the outlook is not good

In recent years the impression is gaining that x ray treatment may provide unexpected benefit in the prevention of refilling *of the cyst once it has been drained surg*ically

BRONSON S RAY
GEORGE J HEUER

PITUITARY ORGANOTHERAPY

Endocrinology has great possibilities for explaining the vagaries of growth sex and metabolism yet lends itself to two dangers one the popularization of the subject and *the other* the tendency *of* clinicians to draw on their fancy both as regards symptoms and treatment Our knowledge concerning the therapy of hypophysial disease has by no means kept pace with the advance in knowledge of pituitary dysfunction and too little is known of biochemical products on *which we pin our chief hope*

Posterior lobe extract—pituitrin—has marked transitory effects on cardiovascular respiratory and renal systems as well as on metabolism smooth muscle and certain glandular structures Separation of the product into pitocin (oxytocin) and pitressin *has not been entirely satisfactory* and their physiologic effects overlap Clinically these preparations are variously used by obstetricians to cause uterine contraction and aid in the expulsion of the fetus or placenta also to control hemorrhage and overcome atony No particular clinical advantage has been shown from the use of pitocin Pituitrin and pitressin have a limited use in stimulating bowel action and allaying abdominal distention

Pituitrin because of its antagonistic action on insulin has found use in helping to overcome the effect of hyperinsulinism Its antidiuretic properties are employed *to ad*

vantage in treating diabetes insipidus but the action is transitory and continued usage is necessary Convenient preparations for nasal spray and snuffing are obtainable

But aside from these uses of posterior lobe preparations one cannot definitely assign to them any physiologic role in the treatment of disease of the hypophysis

In the preparation and use of anterior lobe and whole gland extracts there has been only limited success Various growth hormones are on the market but in an uncertain state of purification and not yet officially recognized Beneficial results are reported from their usage during the growth period but growth is not stimulated at a rate sufficiently above normal to rehabilitate the dwarf and even the most enthusiastic admit that a more potent extract is to be desired if it is to find wide use in clinical medicine It is one thing to transplant gland tissue daily to a laboratory animal and another to put the principle to clinical use

The sex maturing hormones prepared from the gland itself so far have had no value However following the discovery of anterior pituitary like hormone in the urine of pregnancy—prolan—preparations from this urine have appeared on the market and attained wide vogue in the treatment of conditions supposedly the result of deficiency in gonadotropic hormone The beneficial results obtained from these preparations in some cases of functional uterine bleeding warrant their trial but their employment in endocrinopathic amenorrhea alone has no value Beneficial and sometimes striking results have followed their use in some cases of undescended testicle not the result of a mechanical defect

The value of any of the pituitary preparations in the treatment of other pituitary deficiencies besides those mentioned is questionable The fact that in no instance has the more or less blind usage of these extracts led to definitely harmful results testifies to their lack of potency The oral administration of pituitary preparations is looked upon by most investigators as useless and the cost of repeated injections of the comparatively expensive extracts over months and years is prohibitive to most patients Much of the overenthusiasm on the question of pituitary extracts is to be deplored yet no doubt some day, aided and abetted by their intelligent employment meanwhile, perfection of these preparations will be attained

In contrast to the unsatisfactory results in the use of whole pituitary substance are the brilliant successes in the use of purified and synthetic substances employed in the treatment of disturbances in the peripheral endocrine glands Thus the secondary deficiencies of the other glands in dyspituitary states often can be dealt with by substitution therapy The most useful of the substitution products at present are thyroid, parathyroid, insulin adrenalin adrenocortical hormones testicular and ovarian steroids diethylstilbestrol, methyltestosterone and dihydrotachysterol Thyroid and testosterone in small amounts are thought to stimulate the pituitary gland while large doses of gonadal hormones probably inhibit it The ramifications of the use of substitution therapy in pituitary disease are too complex to discuss here but the indications and methods of administration are rapidly being established and the reader will find ample accounts in current writing

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DISEASES OF THE SUPRARENAL GLANDS

The suprarenal glands were first described by Eustachius in 1563 Despite much speculation and considerable investigation no true inkling of their function was apparent until the memorable studies of Thomas Addison culminating in 1855 in his classic description of the disease which now bears his name morbus addisonii This probably represents the beginning of endocrinology since his discoveries directed medical thought and effort into new and fruitful channels In the following year Brown Sequard showed that these glands were essential to life and Vulpian the discoverer of the chromaffin system, demonstrated in them the presence of a substance probably adrenalin which turned greenish on contact with ferric chloride Physiologic studies by Oliver and Schaefer in 1894 demonstrated the vasoconstrictor and pressor properties of the medullary extracts the chemical nature of which was studied in turn by von Furth and by Abel the latter in 1897 preparing a physiologically active monobenzoyl derivative of epinephrine from the suprarenal medulla This was followed by the isolation crystallization and purification of the adrenalin base by Takamine and Aldrich the structural formula being determined by Jowett in 1904 and its synthesis effected in the same year by Stokes The cortical hormone the substance essential to life has eluded the chemist until quite recently when a mildly active aqueous extract was prepared by Rogoff and Stewart (interrenin) and by Hartman (cortin) However the most potent extract was isolated in 1930 by Swingle and Pfiffner who used lipoid in place of aqueous solvents Their extract is capable (1) of prolonging the lives of adrenalectomized animals indefinitely (2) of restoring morbund adrenalectomized animals to the normal state and (3) of overcoming the clinical manifestations of hormonal deficiency in patients with Addison s disease The essential cortical hormone is concerned with water distribution in the body sodium metabolism with blood volume and circulatory efficiency with appetite nutrition digestion the assimilation of food and with energy transformation The active hormone is still unknown though desoxycorticosterone (Reichstein) probably approaches it in chemical structure and physiologic activity In all probability there are several hormones

The cortex of the adrenal gland is concerned in some way with the development and function of the gonads as evidenced by sex changes occurring in patients suffering from cortical tumors These sex anomalies will probably find their explanation in the bisexual anlage and in the chemistry of the hormones concerned *i.e* adrenosterone androgens and estrogens Some interrelation exists also between the function of the adrenal and the pituitary glands

ADRENAL HEMORRHAGE IN THE NEWBORN

Hemorrhage into the adrenal in the newborn usually results in death It is rarely diagnosed except at autopsy Eighty-one cases appear in the literature 11 of which were diagnosed during life Endocrine dysfunction is evidenced by rapid respiration high temperature rash (purpura or petechiae) convulsions cyanosis and gastrointestinal disturbances such as vomiting diarrhea and abdominal pain The concomitant hemorrhagic symptoms are evidenced by (*a*) shock and collapse weak small and irregular pulse air hunger, increased pallor (*b*) distended abdomen with a boggy sensation to touch and a palpable tumor in one or both renal areas The treatment consists of intravenous injection of cortical extract of saline and of 10 per cent glucose solution

LEONARD G ROWNTREE

TUMORS OF THE SUPRARENAL GLAND

In order to understand the tumors of the suprarenal glands it is essential to know something of the anatomy and histology of the glands and more particularly the cytology and origin of the cells concerned since the type of cell present may determine the nature of the clinical manifestations encountered in the individual case The gland consists of two portions the cortex and the medulla which are of different embryonic

origin The medulla is made up of chromophile cells from the embryonic sympathetic nervous system and the cortex of epithelial cells arising from the wolffian body

Cortical Tumors —Tumors of the cortex of the suprarenal lead to the 'syndrome genitosurrenale in the fetus to congenital pseudohermaphroditism, in the infant, to pubertas praecox and in the adult to virilism and hirsutism The age at which the tumor develops is crucial in determining the extent of the changes induced Prenatal overactivity brought to bear on an underdeveloped organism brings about such extreme changes as pseudohermaphroditism while the same influence operating in adult life causes moderate hypertrophy of the clitoris hirsutism and virilism

Pseudohermaphroditism more frequent in the female consists in marked overgrowth of the clitoris which comes to resemble the penis with concomitant suppression of growth of the uterus and ovaries

Infantile pubertas praecox is more frequent in the male It is characterized by premature and excessive development of the sex organs and early appearance of secondary sex characters Thus a male infant of thirty months may exhibit genitalia of adult proportions voice changes and profuse coarse pubic hair In addition to genital changes a tumor may be felt in either flank Metastases are common especially in the joints and when present bespeak a bad prognosis Such tumors developing in young girls usually lead to hypertrophy of the clitoris and to increased growth and male distribution of hair

Virilism and Hirsutism —The incidence of cortical tumors in adults is higher in women Clinically the patients tend almost invariably to become more masculine The skin becomes coarse greasy and often presents an acneform rash The growth of hair is stimulated particularly of the beard and mustache The pubic hair partakes of male distribution The clitoris tends to enlarge the uterus ovaries and breasts to atrophy In the course of a few months an erstwhile beautiful woman may assume the appearance of a coarse, hairy and rather loathsome male the voice becoming masculine Such tumors occurring in men usually lead to increased masculinity but in one of Holl s cases feminism developed in a man past forty years of age, marked hypertrophy of the mammary glands atrophy of the testes and penis loss of libido and potentia and reversal of sex interest

The *treatment* of these cortical tumors is surgical removal of the tumor, which if undertaken prior to the development of metastases may result in absolute and permanent cure and a complete disappearance of all abnormal clinical manifestations Probably the most interesting case of this type in the literature is that described by Gordon Holmes This patient observed for two years prior to operation presented the typical picture of hirsutism and virilism and within a few months after operation was completely restored to normal and still remained so nine years later One of our own patients similarly recovered within a year after operation

Formerly surgical treatment of these tumors was associated with great risk collapse and death frequently resulting from hormonal deficiency within a few hours or days after operation This is probably best explained on the hypothesis that owing to the assumption of adrenal function by the tumor cells themselves the function of the contralateral or normal gland is suppressed The removal of the tumor deprives the body of its supply of cortical hormone The temporary administration of cortical extract (Swingle) or desoxycorticosterone acetate by way of substitution therapy and of sodium chloride is desired until the remaining adrenal resumes its function

Radiation of the gland through deep x ray therapy or by radium may prove helpful temporarily where operation is contraindicated because of metastasis or for other reasons

In connection with these tumors the displacement of the contiguous kidney best appreciated through pyelography is of diagnostic importance Certain clinical phenomena are of unusual interest and deserve further investigation (1) the tremendous increase in appetite and in body weight which may accompany the metastasizing tumor (2) the concomitant development of hypertension which may disappear as a result of removal of the tumor (3) the coexistence of cortical tumor and the clinical

manifestations suggestive of Addison s dis ease—brownish pigmentation of the skin, extreme exhaustion, and in certain cases emaciation

Medullary **Tumors**—The immediate anlage of the suprarenal medulla lies in the sympathetic ganglia which are themselves derived from the neural crest Medullary tumors are of three varieties depending on the type of cell from which they arise All are rare

Neuroblastomas—These are of three types that described (1) by Pepper char acterized by metastases to the liver and lungs or to the abdominal lymph nodes (2) by Hutchinson characterized by metastatic involvement of the orbit skull and long bones, recognized therefore most frequently by orthopedic surgeons or roentgenologists and (3) by Goldzieher characterized by marked anemia suggesting the pernicious type Hutchinson s variety is relatively the most frequent It runs a rapid and fatal course and metastasizes freely particularly to the scalp skull and vertebrae

Ganglioneuromas are benign and occur usually prior to the twentieth year

Paragangliomas consist of chromaffin type of cells and may occur where chromaffin cells exist These tumors were first described by Rabin in 1892 since then about thirty cases have appeared in the literature They are accompanied not infrequently by intermit tent paroxysmal hypertension

One of my patients is of unusual interest in this connection as the surgical removal of the tumor was followed by immediate complete and permanent recovery The pa tient a young woman thirty years of age was admitted complaining of peculiar spells The paroxysmal attacks had com menced one and one half years previously and were increasing in frequency and se verity occurring once or twice daily and lasting from one half hour to three or four hours The spells were preceded by discom fort in the epigastrium followed by dyspnea occipital headache tachycardia palpitation vomiting and peculiar blanching of the skin particularly of the face Observation in an attack revealed hypertension a systolic pres sure of over 300 mm of mercury with nor mal blood pressure between The tumor on removal proved to be a paraganglioma This constitutes the first complete clinical record with cure Since this report, similar cases with successful removal of the tumor have been reported by Shipley and Pincoffs and by Porter and Porter The presence of epi nephrine in the tumor removed by Shipley was demonstrated by Professor Schultz

Although the hypertension accompanying paragangliomas is usually intermittent in type it may become continuous The clinical picture observed during these spells so closely resembles malignant hypertension that it would seem desirable to reconsider the whole question of the relation of the adrenals to hypertension

Intermittent hypertension has also been observed in association with cortical tumors accompanied by clinical manifestations of hirsutism and virilism (Oppenheimer and Fishberg) In one of these cases autopsy revealed a tumor involving both the adrenal cortex and the medulla The removal of such a tumor by Murray and Simpson resulted in complete relief both from virilism and from hypertension the systolic blood pres sure dropping from 200 to 130 mm of mer cury although it continued to rise abnor mally under stress and strain

The *treatment* of these tumors is surgical The use of cortical extract or hormone and of sodium chloride decreases the surgical risk and greatly enhances not only the prospects of the individual patient but also an effec tive understanding of the various types of cells and their function in the organism The correlation of clinical pathologic and histologic findings is urgently needed in all tumors of the adrenal glands Similarly such correlations are essential in all tumors ac companied by virilism and hirsutism among which should be included pituitary bas ophilism tumor of the kidney (hyper nephroma) tumor of the ovary (arrheno blastoma) and the oat cell tumor of the thymus gland

LEONARD G ROWNTREE

HYPOFUNCTION OF THE ADRENAL GLAND —HYPO ADRENALISM OR HYPO ADRENIA

The clinical syndrome involving exhaus tion chronic fatigue emaciation low basal metabolism low blood pressure and loss of libido and potentia is often diagnosed hypo

adrenalism or hypo adrenia The justification of such a diagnosis is questionable Two such cases so diagnosed by prominent internists were subjected to treatment with cortical hormone in amounts sufficient to control Addison s disease Both failed to show improvement Since epinephrine is likewise ineffective further evidence implicating the adrenal is needed

LEONARD G ROWNTREE

ADDISON S DISEASE

(*Morbus Addisonii*)

Definition — The leading and characteristic features of the morbid state to which I would direct attention are anemia a general languor and debility a remarkable feebleness of the heart s action irritability of the stomach and a peculiar change of color of the skin occurring in connection with the diseased condition of the suprarenal capsule (Thomas Addison 1855)

Etiology —The remote cause of the disease from the practical point of view is tuberculosis of the gland in 80 to 90 per cent of the cases and atrophy of unexplained origin in 10 to 20 per cent The immediate cause of the clinical manifestations is deficiency of the cortical hormone which appears when approximately four fifths of the gland substance is destroyed by pathologic processes Syphilis coexists in a not inconsiderable proportion of cases Its etiologic relationship to Addison s disease is still a matter of controversy Amyloidosis is occasionally concerned Other causes frequently assigned are of almost negligible consideration namely carcinoma mycosis fungoides and lesions involving the semilunar ganglion, the solar plexus and the abdominal sympathetic chain Hemorrhage and infarction play a role in the newborn

The disease is rare about sixteen cases per 100 000 admissions in the Mayo Clinic It is twice as common in the male as in the female and is most frequent between the ages of thirty and fifty According to the mortality statistics of the Bureau of the Census its incidence has decreased approximately 33 per cent since the beginning of the century It is now 0 3 per 100 000

Morbid Anatomy —Bilateral fibrocaseous tuberculosis was found in fourteen of fifteen cases by Hedinger, in twenty two of twenty nine cases by Conybeare and Mills and in twenty six of thirty one of our cases studied by Nelson W Barker The bacillus of tuberculosis was demonstrated in eleven of our fourteen cases studied within five years of death As a rule the glands are found to be definitely enlarged sometimes weighing from 20 to 30 Gm (normal 4–10 Gm) Complete calcification is not frequent, although marked increase in calcium may be easily shown roentgenologically during life and by chemical analyses at necropsy

One case of atrophy was observed by Addison Bittorf reviewed thirty such cases described in the literature Conybeare and Mills described six cases in 1884 Brenner five in 1923 and we have studied six The cause has been ascribed to simple atrophy secondary to necrosis from some toxin with specific affinity for the suprarenal cortex (Brenner) Congenital hyperplasia and lesions of atypical tuberculosis and syphilis have also been suggested by others In one of our cases the possibility of injury from x ray was considered Complete absence of the adrenal glands has been described at times In one of our cases no glands could be located except on serial section of the tissues concerned

Tuberculosis, healed or active lesions, existed elsewhere in all our cases of adrenal tuberculosis as pulmonary tuberculosis nodules in the lungs or lymph nodes of the hilum pleural adhesions genito urinary tuberculosis or osseous tuberculosis particularly of the spinal column Active tuberculosis was absent in all of our cases of atrophy but in two healed lesions were found Tuberculous involvement of the chromaffin system contiguous to the medulla is not frequent

The heart is disproportionately small in a large majority of the patients with Addison s disease This is commonly ascribed to brown atrophy It may in our opinion represent a primary result of hormonal deficiency rather than the atrophy of disuse to which it is commonly ascribed The thymus and lymph nodes are occasionally enlarged especially in the presence of adrenal atrophy Pigmentation is seen at times in the serous membranes

Physiopathology.—Recent investigation concerning the function of adrenal cortex has been immeasurably helped by advances in our knowledge of the chemistry of the cortex *In all some twenty four different* sterone compounds have been isolated Desoxycorticosterone has been synthesized by Reichstein An extract of the adrenal cortex such as Swingle s probably contains a large number of closely related steroid derivatives which have specific effects differing from one another quantitatively and qualitatively Desoxycorticosterone has been chiefly utilized in the investigation of the adrenal cortex It exercises marked control on the metabolism of sodium chloride and potassium but does not affect the carbohydrate mechanism to any great degree

While much yet remains to be learned, it is probably safe to say at present that the suprarenal cortex participates in some way in the control of water metabolism the state of hydration in the organism the fluid distribution and the volume of the blood the electrolytic content of the organism and especially in the physiological activity of sodium and potassium capillary permeability carbohydrate metabolism circulatory efficiency muscular function and the renal function particularly as it relates to the excretion of sodium chloride and potassium *The adrenal cortex favors the retention of* sodium and water while increasing the secretion of potassium

In the crises of adrenal insufficiency there occur dehydration hemoconcentration decreased blood volume lowering of the level of the sodium ions in the blood and a resulting state of shock characterized by circulatory failure (low blood pressure) increase in the level of blood urea nonprotein nitrogen sulfates and potassium etc Under these conditions the administration of salt water and above all cortical extract or hormone is essential to the best interests of the patient

Symptoms.—The disease usually presents three stages (1) unexplained weakness and exhaustion following upon some upper respiratory infection (2) the typical clinical syndrome so easily diagnosed (3) collapse in which nausea vomiting dehydration and toxemia dominate the picture

The onset is usually insidious occasionally acute The most prominent symptoms and signs in their usual order of appearance are (1) asthenia and fatigue (2) pigmentation of the skin and mucous membranes (3) anorexia nausea and vomiting (4) loss of weight (5) arterial hypotension (6) dizziness syncopal attacks (7) collapse with dehydration and circulatory failure

Asthenia debility and languor are usually the earliest symptoms However unexplained pigmentation may develop and persist for some weeks or months prior to the onset of asthenia In such cases the prognosis is unusually good The asthenia is invariably present is both subjective and objective and mental as well as physical in character When pronounced the patient is bedridden The remarkable feebleness of the heart s action is evidenced by hypotension circulatory failure coolness of the body surface fainting spells and dyspnea Mild hypotension is usually present throughout the disease systolic pressure being as a rule in the neighborhood of 90 to 100 and the diastolic 60 to 70 mm of mercury In the terminal phases and the crises the systolic pressure is often decreased to the neighborhood of 60 mm of mercury When hypertension has existed prior to the illness the blood pressure may remain elevated or normal until within a few hours of death

Gastro-intestinal Symptoms—The gastro intestinal symptoms are usually pronounced and include nausea vomiting gaseous distention and occasionally periods of intense diarrhea Nausea may be continuous but is usually more pronounced in the morning As the disease progresses vomiting becomes more marked so that little or no food is retained A striking loss of weight often 40 to 50 pounds results Because of retained elasticity the skin constantly fits snugly despite the weight loss hence emaciation has been underestimated by the majority of clinicians

Pigmentation of the Skin and Mucous Membranes—The most striking visible manifestation of Addison s disease is the pigmentation of the skin Attention is often called to it by friends and relatives who think the skin looks dirty It is frequently ascribed by patients to tanning by the sun a tan which fails to disappear on removal from exposure Addison described it as a

dingy or smoky appearance of various tints or shades of deep amber or chestnut brown *Pigmentation is most marked over* the exposed parts the face, neck and hands, at the points of pressure the buttocks, the elbows, the knees and at the points of contact with clothing corsets garters etc The palms of the hands and soles of the feet usually escape except for the creases Pigmentation of the genitalia is usually excessive Jet black freckles are very common especially on the backs of the ears A gray or white scurf is often seen over the pigmented areas particularly those on the elbows and knees

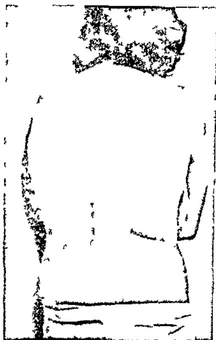


Fig 163—Addison s disease in a thirty two year old white female Note the scattered areas of pigmentation to the right of the dorsal spine and the diffuse pigmentation near the right flank (Courtesy of Dr H David Markman)

Pigmentation of the Mucous Membranes—This is of great diagnostic importance when accompanying pigmentation of the skin The addition of pigmentation of the mucous membrane of the mouth the lips the gums, the inner sides of the cheeks and on the tongue tremendously increases the probability of Addison s disease It is usually brownish or black in color although bluish tints are not *at all uncommon* particularly on the tongue

The cause of the pigmentation is not well understood The pigment itself is melanin Bloch suggests that pigmentation is due to the presence of a specific oxydase in the skin, which forms melanin from dioxyphenyl alanine (dopa), and has devised a biopsy test based on this assumption

Pain in the loins is more frequent than is usually realized As a rule it is dull and paroxysmal in character but occasionally it is intense the patient *groaning constantly* and holding a rigid abdomen

Nervous and mental symptoms are usually lacking though a psychosis due to exhaustion or toxemia is not infrequent Restlessness is apparent and apprehension is extreme at times the patient tossing about and apparently incapable of finding a position of rest

Sex changes are neither frequent nor marked Dysmenorrhea is not uncommon in the female and, when present is usually associated with marked menstrual exacerbations of the addisonian symptoms In the male there is a tendency to loss of libido and potentia Occasionally sex activity is *maintained and healthy children may* be born of fathers suffering from Addison s disease Conception is usually followed by abortion

Course—Addison s disease usually pursues a gradually downward course with striking remissions and acute exacerbations which may attain the severity of a crisis Crises and death often follow stress and strain overexertion exposure acute infections surgical procedures or administration of purgatives low salt or high potassium intake Occasionally the onset is acute and *the course short and rapid* Excruciating pain noisy delirium and dyspnea may precede death The shortest duration on record is eighteen days a dozen or so patients have survived ten years Remission simulating recovery has been encountered in two cases of Addison s disease where the clinical diagnosis was beyond question suggesting the possibility of temporary suppression of the function of the adrenals With modern methods of treatment *remissions are more* frequent pronounced and prolonged However the course is usually chronic nausea and vomiting become more pronounced and asthenia more marked until the patient is completely bedridden Eventually the eyelids droop the mouth hangs open drowsi

ness becomes more marked and the limbs hang limp The patient takes the contour of the bed and assumes the picture of complete exhaustion and helplessness The fire burns lower and lower, interrupted occasionally by fitful flickerings of life and consciousness until death ensues

Diagnosis —The diagnosis can usually be made on clinical grounds (1) progressive asthenia (2) gastro intestinal irritability (3) pigmentation of the skin and mucous membranes (4) feeble heart action especially as heard with a stethoscope (5) low blood pressure and (6) the occurrence of these symptoms in a patient who has or has had tuberculosis Complications often confuse the picture and result in failure to make a correct diagnosis

Laboratory findings of importance are (1) demonstration of melanin in the skin by biopsy (2) decrease in the sodium content in the blood below 130 milliequivalents, (3) increase in the blood urea nonprotein nitrogen sulfates and potassium in the blood, (4) decrease in the blood volume and hemoconcentration (5) decrease in basal metabolism (6) roentgenologic evidence of calcification in one or both adrenal areas

Where doubt exists resort may be had to (1) the effects of restricted sodium intake (2) the effects of a high salt diet (3) the administration of cortical hormone as a therapeutic test

In arriving at a diagnosis difficulty is often encountered in relation to pigmentation The greatest difficulty is on racial grounds Ethiopians Orientals, American Indians Levantines and Latins normally may show pigmentation which in light skinned individuals would be characteristic of Addison s disease In the Nordic the pigmentary quartet dermal buccal and labial pigmentation with the presence of jet black freckles is practically pathognomonic

In differential diagnosis metallic poisoning must be excluded particularly lead arsenic and silver In *acanthosis nigricans* the pigmented areas have the appearance and the feel of velvet rather than of satin as is found in Addison s disease The discovery of abdominal malignancy is of primary importance Hemochromatosis should be recognized through the presence of sugar in the urine and the enlargement of the liver Pregnancy sometimes offers a diagnostic problem Scleroderma should offer no difficulty although it is frequently accompanied by skin pigmentation which is very suggestive of Addison s disease In all these diseases skin biopsy should prove helpful Leukoderma frequently accompanies Addison s disease and its presence does not exclude the existence of Addison s disease Carotinemia and jaundice can be recognized through the presence of the abnormal pigmentation in the serum Cholasma malaria exophthalmic goiter and vagabond s disease should not offer undue difficulty Extreme weakness from other causes such as neurasthenia and postinfluenzal exhaustion is frequently considered early in the course of the disease



Fig 164 —Addison s disease Flat plate of abdomen showing almost complete calcification (presumably tuberculous) of left adrenal gland and beginning calcification of right adrenal (Courtesy of Dr H David Markman)

Complications —Tuberculosis in one form or another is present in 80 to 90 per cent of the cases and is a matter of paramount importance from the standpoint of diagnosis prognosis and treatment Syphilis frequently coexists and its treatment in the presence of Addison s disease should be along extremely conservative lines The incidence of leukoderma is higher than that of mere chance Upper respiratory infections and in fact infections of all kinds are dangerous because of the exacerbations induced

Prognosis—The prognosis in Addison's disease has been always and should continue to be regarded as extremely grave It is now largely the prognosis of tuberculosis This holds true regardless of the excellent immediate results from the use of extra salt or of cortical hormone In order to arrive at a prognosis the history of the case the clinical condition of the patient the location and activity of the tuberculosis, the laboratory findings the immediate response to treatment and the economic situation should all be considered

The indications for a grave prognosis are collapse extreme asthenia lowered bodily and surface temperature protracted vomiting extreme loss of weight, a sodium level of less than 130 milliequivalents systolic blood pressure of less than 70 mm of mercury, *concentration of urea of more than* 60 mg per 100 cc of blood a short rapid course without much pigmentation poor response to treatment, and the presence of active tuberculosis The most important single clinical prognostic index is the body weight only those who eat and gain weight, recover A dozen or more cases have been reported as surviving ten years or more The author has had three cases which have survived fifteen years or more Mildness of the disease and wise management rather than specific treatment would seem to be responsible for these results However with better and more modern treatment the prognosis is improving and when adequate cortical extract is available death from hormonal deficiency should be largely preventable

Treatment—The treatment of Addison's disease during the last decade has undergone radical changes with the introduction of an active cortical hormone and the recognition of the importance of salt Now as always emphasis must be placed upon adequate rest warmth control of activities and the avoidance of stress and strain purgation and exposure to cold Whereas formerly the management of this disease exhausted the therapeutic skill of the physician today with the use of cortical extract or hormone and a diet rich in salt the patients may be relatively free of symptoms Formerly the patient was more or less continually in a crisis while now he is often a semi invalid or even a fairly active ambulant patient capable of conducting considerable business Obviously the care of the underlying tuberculosis, if present is of paramount importance

Substitution Therapy.—The cortical extract of the adrenal gland as prepared by Swingle and Pfiffner, usually controls the clinical manifestations of adrenal insufficiency immediately if given in adequate amounts Of this preparation 1 to 5 cc daily given parenterally or 1 to 2 cc of a three- to five times concentrate given on alternate days usually suffices Unfortunately, this preparation is not generally available Eschatin a commercial product is less potent and should therefore be used in larger amounts In the terminal phases of the disease in crises, during intercurrent infections and when surgery is undertaken, the dose should be increased two to five times and *the extract given intravenously No danger* attends these larger amounts but unfortunately the cost of such treatment is often prohibitive As a matter of safety it is wise to employ cortical extract in small amounts on alternate days even during periods of remission This simple rule will prevent many deaths It should be remembered that large amounts of salt daily tend to decrease the need of cortical hormone thus permitting its use in smaller dosage

Salt Therapy—Sodium chloride has been found of unquestionable value in the treatment of this disease The diet should be rich in salt and in addition 5 to 10 Gm of sodium chloride may be given daily in the form of compressed tablets or capsules Sodium also in the form of sodium bicarbonate or citrate may be added up to 2 to 5 Gm daily Salt therapy is of special value because of its ready availability Because it decreases the hormonal need it renders the treatment of Addison's disease less expensive It must be remembered however that salt alone will not suffice To rely on salt alone is to court disaster

Combined Cortical Extract and Salt Therapy—This constitutes the best form of therapy to date With this regimen good results are almost uniform and the survival time prolonged The last five successive cases subjected by the author to Swingle's preparation of cortical extract and to high salt intake are all alive and comparatively well averaging almost nine years survival and

seven years on treatment All five are fairly well rehabilitated *

Foods rich in potassium should be avoided Water may be almost as important as salt *especially in overcoming dehydration* and during crises Loeb states that six of his patients have died a classic Addisonian death with a perfectly normal electrolytic pattern in their blood with the exception of dehydration '

Combined cortical extract and salt therapy thus offer tremendous advantages and should be employed in all cases throughout the whole course of the disease *Very occasionally* with adequate hormonal replacement the need of sodium and water is imperative In periods of crisis sodium chloride in 1 to 3 per cent solution should be used freely intravenously or normal saline with glucose up to 4 liters per day

Treatment with Desoxycorticosterone Acetate—Reichstein has not only isolated a crystalline hormone from the adrenal cortex but has synthesized desoxycorticosterone acetate which is potent both experimentally and clinically This product injected in sesame oil in doses of 5 to 10 mg daily, is now undergoing extensive clinical trial and is strikingly effective in many respects However its use or abuse may be attended with serious danger if salt therapy is also pushed *too vigorously* This may result in hypertension generalized edema and cardiac failure

A new method of administration is undergoing clinical trial by Levy Simpson in England and in this country by Thorn and his collaborators namely the surgical implantation in the fatty tissues of the back of pellets of this preparation which undergo continuous *absorption thereby supplying* the hormonal need of the patient over weeks or months While this pellet treatment is not generally available for general use the results obtained by Thorn have been most encouraging Desoxycorticosterone acetate in propylene glycol administered sublingually (7 drops held under the tongue for fifteen minutes seven times daily) is mildly helpful especially when combined with salt therapy This method is unduly costly

* One patient succumbed since this article was written having been under my care over a period of ten years

The effects of treatment may be summarized as follows the disappearance of nausea and vomiting the appearance in their place of hunger normal gastro intestinal activity *increase in weight* decrease in *pigmentation* increase in blood pressure (slight and delayed), access of hope and euphoria, increase in bodily resistance, and a desire to return to normal activity

The significant changes in laboratory findings are gain in weight with positive nitrogen balance increased level of blood sodium increased blood volume where it *has been depleted increase in basal metabolism* where it has been seriously depressed improved renal function with disappearance from the blood of undue accumulations of nitrogen urea sulfates etc The results in Addison s disease suggest that the cortical hormone exercises a fundamental influence from the standpoint of food ingestion and utilization The psychic effects of treatment are often as profound as the physical

In a large sense these results may be regarded as immediate in character the correction of hormonal deficiency and not as a cure of the disease which in the vast majority of instances is tuberculous in origin Occasionally failure to relieve hormonal deficiency is encountered particularly where the disease is far advanced Even in mod*erately ill patients inexplicable* resistance to substitution therapy is encountered at times Under such conditions the possibilities of both hormonal and sodium therapy should be exhausted

Dehydration may be primarily from hormone deficiency or secondary to continuous vomiting or diarrhea Fluids should be administered intravenously, or subcutaneously *as saline or glucose solutions They should* be used promptly and freely in crises as they often prove to be life-saving

Adrenal transplants have been almost universally unsuccessful but a glimmer of hope has been recently brought in to this field by E M Auslander who claims some success in fourteen cases thus treated

The Control of Tuberculosis—This now assumes larger proportions It *demands* often the consultation with some one expert in the diagnosis and general management of tuberculosis The nature and care of the local lesions must also be considered Here

tofore, the operative risk has practically excluded surgical treatment of tuberculous lesions of the gland itself or of genito urinary or osseous tuberculosis but since the advent of cortical hormone this difficulty has been largely overcome and patients may now be subjected more safely to surgical procedures if indicated In the management of the tuberculosis of the adrenal glands themselves, the judicious use locally of deep x ray therapy may be tried together with the administration of calcium and viosterol

LEONARD G ROWNTREE

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DISEASES OF THE THYMUS GLAND

Definition—This subject could well be defined as The Thymus Problem Many functions have been attributed by various investigators to the thymus gland only to be denied by others and there has been much uncritical controversy concerning the symptomatology and treatment of disturbances of it Some of the functions which from time to time have been supposed to be carried on by the thymus are (1) influence on osseous development and regulation of calcium and phosphorus metabolism in health and in certain diseases of the bone (2) regulation of blood pressure (3) effect on coagulation of the blood (4) action as a reservoir of phagocytic cells (5) significance as part of the lymphatic system and (6) its influence on growth and development None of these possible functions has any relation to clinical practice in diagnosis and treatment That is to say no means are available to modify any such functions and no extract of the thymus gland has been used in human beings with any proved effect

Morbid Anatomy—The studies of Hammar Greenwood Boyd and others have clearly shown that earlier ideas and statements concerning the size of the normal thymus were erroneous They have demonstrated that the size varies correspondingly with the general nutritional state of the body that in acute illness and temporary inanition the organ decreases rapidly in size although there may be little loss of general body tissue and that even under normal conditions its dimensions and weight vary greatly Without detailing the weights usually found it may be stated that at no time of life can a weight of 30 Gm be considered enlargement and that during the period of growth weights of 50 Gm are within the limits of variability

Where there is actual enlargement it usually consists of simple hyperplasia in which medulla and cortex ordinarily share equally Hyperplasia may occur in exophthalmic

goiter and in acromegaly and there is an implication here that the thymus is a part of the endocrine system although the relationships are far from clear A nonmalignant enlargement associated perhaps with lesions in the suprarenal cortex may occur in myasthenia gravis and at times enlargement is present with other myopathies

Symptoms —With the exception of those to be specifically noted symptoms which have been attributed to alterations in the thymus are confined in age incidence to infancy and usually to the first few months of life

Pressure Symptoms —Can a normal or hypertrophied thymus compress the trachea the recurrent laryngeal nerve and certain blood vessels and cause symptoms such as dyspnea and suffocative attacks (thymic asthma) brassy cough and cyanosis? In favor of the possibility of pressure are (1) The demonstration through the bronchoscope or by lateral roentgenograms that tracheal compression may occur (2) the apparent cessation of symptoms after radiologic treatment of the thymus and (3) the occasional finding at necropsy which suggests that compression had occurred during life On the contrary it is evident that (1) It would be difficult for a soft organ such as the thymus to compress the cartilaginous trachea (2) that great neoplastic enlargement may occur without symptoms of compression (3) that there is no close correlation between the symptoms which might be attributed to pressure and the size of the roentgenographic shadow and (4) that careful clinical study will show other causes for such symptoms as dyspnea and cyanosis in most cases The answer probably belongs —as it usually does in such controversy—somewhere between the two extremes and it would appear possible that *rarely* an enlarged thymus may press on structures in the superior thoracic aperture and cause the symptoms described

Status Thymicolymphaticus —It is evident that the state of the thymus gland and lymphatic structures originally described as enlarged and associated with so called lymphatism actually represented only the normal structures in well developed subjects who died suddenly from some other cause Sudden death is not related to enlargement of the thymus as many studies have shown If there is any connection between sudden death and this organ it cannot be explained by such vague terms as hyperthymization or lymphotoxemia ' It remains to be proved whether the thymus might be secondarily affected by suprarenal insufficiency or in some other way and thus be directly concerned in certain rare instances of sudden death associated with hypoglycemia and rapid fall in blood pressure

Endocrine Symptoms —That the thymus is an endocrine organ is suggested by several facts for example adrenalectomy suprarenalectomy and gonadectomy are followed by delayed involution or hyperplasia of it These observations do not prove an incretory function since other types of tissue than those of the endocrine system might be so affected A hyperplastic thymus however may be found in pluriglandular syndromes involving the gonads the thyroid the suprarenals and the pituitary The experiments of Rowntree Einhorn and others have aroused new interest in this phase of the thymus problem Briefly these have shown that in the offspring of thymectomized rats a definite retardation of growth occurs as reflected by body weight and body length Furthermore after continuous intraperitoneal injection into rats of a thymus extract prepared by Hanson successive generations of their offspring show acceleration of growth and development

Some endocrinologists have described in association with persistence of thymus during adolescence and into adult life a type of person who is tall slender and loose-jointed exhibits fine texture of the skin a tendency to eczema scanty hair poor resistance to infection has thin walled blood vessels becomes easily fatigued and shows inferiority in the development of circulatory and endocrine organs It is not clear that if the persons so described have an enlarged thymus this is a relationship of cause and effect the combination may be but part of a syndrome due to some underlying cause probably of a pluriglandular nature Timme has termed the condition status hypoplasticus

Other Symptoms Sometimes Attributed to the Thymus —There is no good

reason to believe that so called "holding the breath spells' are associated with thymic hypertrophy That hypersusceptibility to disease is related to thymic dysfunction is only an hypothesis A possible connection between pylorospasm and the thymus has been postulated from time to time, the explanation being given that the enlarged thymus and the pylorospasm are dependent upon vagotonia, the result of insufficient suprarenalin production

Diagnosis—When such symptoms as dyspnea suffocative attacks brassy cough and cyanosis exist and no other cause can be found the question of thymic hyperplasia arises How can the presence of this be shown? Certainly the average clinician is seldom able to convince himself that he can outline an enlarged thymus by percussion nor can he often palpate it in the suprasternal notch If impaired resonance can be elicited over the manubrium this might be due to other intrathoracic structures and furthermore it is probably anteroposterior enlargement not lateral which could cause compression *Roentgenographic diagnosis* of an enlarged thymus is by no means a simple matter There is no mathematic formula which proves that the shadow cast is too large for the age or the size of the chest of the individual The size of the shadow is greater during deep expiration than during inspiration, and there are probably racial and geographic differences in the size of the thymus When the weight may vary so greatly under normal conditions it is certain that the roentgenographic shadow will also Lateral roentgenograms taken in both respiratory phases to determine compression or buckling of the trachea, and interpreted by an expert may have some value and perhaps the fluoroscope may occasionally be helpful

In *differential diagnosis* emphasis should be placed on the importance of searching always for some other cause for symptoms Dyspnea suffocative attacks or cough may be caused by foreign bodies cysts papillomata or other tumors in the air passages retropharyngeal abscess and tumors outside the air passages causing pressure on them Other causes for dyspnea which should be eliminated before the thymus is implicated are acute and diphtheritic laryngitis bronchitis, pneumonia, atelectasis asthma and the like Many of these conditions or even nasal obstruction and congenital laryngeal stridor are more likely to be the cause of cyanosis than is enlargement of the thymus It is difficult to believe that enlargement of the thymus or dysfunction of it could result in convulsions and in cases where this symptom has been attributed to the thymus a thorough search would usually have revealed some other condition such for example as meningitis, encephalitis intracranial hemorrhage or particularly in the age period from six months to two years, infantile spasmophilia or tetany

When the history examination or necropsy uncovers no reason for sudden death even though the impression exists that the thymus and lymphatic structures are enlarged, it is probably wiser in the present state of knowledge to conclude that the cause was unknown and not to catalogue it in the waste paper basket of status thymicolymphaticus"

Treatment—The philosophy of the treatment of what appears to be an enlarged thymus can be deduced from the previous statement Partial or total thymectomy may rarely be indicated for neoplastic growth or radiologic treatment may be given As shown by Friedlander radiologic treatment will reduce the size of the thymus There is certainly no reason for employing this form of treatment routinely in newborn infants as has occasionally been recommended and in fact there is no need to take routine roentgenograms of their chests With proper dosage and with protection of other structures there is no harmful result from roentgen or radium irradiation of the thymus The procedure can be allowed, then when careful study fails to reveal any other cause for the symptoms of dyspnea and cyanosis in infants occasionally it appears that such treatment is effective Whether this is coincidental or whether other intrathoracic structures which might have been operative have been decreased in size is not so certain

If obstructive symptoms were due to an enlarged thymus intubation or tracheotomy would not give relief since the tracheal stenosis would be too low to be affected

It can be stated categorically that radiologic treatment of the thymus would not

prevent sudden death even if this organ were in any way implicated There is no reason for radiologic treatment as a routine procedure before operation or anesthesia There is no extract of the thymus which is to be recommended for use in human beings

A Graeme Mitchell

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DISEASES OF THE PARATHYROID GLANDS

TETANY

Definition —Tetany is a result of abnormal inorganic salt metabolism manifested by increased irritability of the neuromuscular system It is a common disease in infancy but relatively rare in adult life Clinically there are distinguished (1) active tetany with tonic spasm of any muscle (more usually bilateral in the extremities and also in the glottis) and occasionally with generalized convulsions and (2) latent tetany which is demonstrated by neuromuscular responses elicited by very mild electrical or mechanical stimuli

Symptoms and Signs —There is a triad of well recognized clinical signs of latent or active tetany *Erb s sign is the most reliable* clinical sign of tetany It is based upon the neuromuscular response to electrical stimuli In both latent and active tetany with the stimulating electrode over a motor nerve there is a muscular response to far weaker stimuli than the minimal effective stimulus needed in normal individuals The cathodal opening response which normally requires more than 6 milliamperes, is obtained with stimulation by less than 5 milliamperes There is also a reversal of normal responses *for contraction occurs in tetany* with a weaker current on anodal opening than that *required for response to anodal closure* The Chvostek sign is easy to elicit It is a twitch *of the innervated muscles following gentle* tapping over the facial nerve at its exit *from the stylomastoid foramen, anterior to* the external auditory meatus The Trousseau *sign is the ability to precipitate a typical* paroxysm of tetany by temporary compression of an extremity either over a principal nerve trunk or, more easily by occluding the arterial blood supply to the extremity

The typical tonic muscular contractions of active tetany come spontaneously The hand becomes stiff with rigid fingers The thumb is markedly adducted and partially covered by the stiff fingers which are usually bent only at their metacarpophalangeal joints The palm of the hand is hollowed while the wrist and elbow are flexed In the lower limbs the toes are flexed and the sole becomes arched like the hand The heel is pulled up and the rest of the leg is fully extended The muscles all feel very tightly contracted Any muscles may be involved particularly those of the face eyes tongue and larynx The sympathetic nervous system as well as the motor nerves may be affected so that smooth muscles such as the bladder intestines and blood vessels are also occasionally involved The contractions are usually tonic in nature and may be prolonged When the glottis and laryngeal muscles contract breathing becomes very difficult with prolonged whistling inspiration and less noisy expiration (called laryngismus stridulus ") and very marked cyanosis Consciousness usually remains unimpaired The spasm may become so severe that breathing is not possible There may also be generalized tonic convulsions which may last for a long time and may result in death These spasms are pre

ceded both in eliciting the Trousseau sign and in spontaneous tetany by a feeling of tingling and diminished sensation marked stiffness, and difficulty of movement of the extremities The contraction after a short time becomes painful and is described by the patient as a cramp In severe tetany it may last for minutes or hours In active tetany other signs are usually preceded by a general sensation of unrest and impending catastrophe

If long continued tetany occurs during the period of growth the teeth are soft and poor and the healing of fractures of bone is said to be slow The lens of the eye is very prone to the formation of cataract

Etiology —The increased neuromuscular irritability which produces tetany is usually dependent upon the following causes

1 Parathyroid deficiency usually follows radical operation upon the thyroid gland with simultaneous removal or damage of several parathyroid glands It then may begin after approximately twenty four hours and may last for days or years Occasionally the disease occurs spontaneously Tetany appears when the calcium content of the blood serum falls from the normal value of 10 to 7 5 mg per cent unless this reduction is due to protein bound calcium (as in the nephrotic syndrome)

2 Inadequate calcium in the diet or persistent fatty diarrhea (steatorrhea or celiac disease) with the excretion of excessive calcium soaps or prolonged and repeated lactation with inadequate calcium intake (formerly called 'nurse s contracture) causes osteomalacia and eventually this progresses to tetany

3 The injection or ingestion of alkaline phosphate salts also produces tetany with a low blood calcium possibly because of the precipitating effect of the phosphate ion possibly because of alkalosis

4 Vitamin D deficiency with the eventual appearance of tetany is not infrequently seen in children and occasionally occurs in adults This may also account for the tetany sometimes seen after prolonged postoperative loss of bile

5 Signs of tetany will result from alkalosis of various origins such as hyperventilation with its resulting uncompensated CO_2 deficit persistent vomiting with its excessive loss of HCl or ingestion of excessive amounts of alkalis

6 Tetany and spasmophilia are not infrequently seen in children less than two years of age They occur more frequently in late winter and spring The recovery from rickets following viosterol administration may be complicated by tetany because of the rapid deposition of calcium phosphate in the bones Convulsions with a very low blood calcium may occur as early as the ninth day of life without evidence of rickets

7 There is a tetany of unknown origin which involves sedentary trades chiefly cobblers and tailors This occurs in epidemics usually in the springtime in central Europe

Diagnosis.—Active tetany is so characteristic that its clinical diagnosis usually offers no difficulty It is distinguished from other neuromuscular diseases by its temporary bilateral spasms and by the characteristic blood findings The three signs of which Erb s phenomenon is the most reliable are also characteristic Final diagnosis of the type of tetany is dependent upon the clinical picture but also upon the laboratory findings summarized in the Table

Prognosis —With recent modern methods of therapy the prognosis of tetany has been greatly improved Acute attacks of low calcium tetany need very careful therapy but by means of intravenous injections of calcium salts patients can usually be kept alive After some days the disease often improves Chronic tetany also has a good prognosis with careful therapy There are of course occasional cases of such severity that the laryngeal spasm or general convulsions result in death

Tetany due to alkalosis has an excellent prognosis With the elimination of the causative factor and ingestion of the needed acid producing salts the tetany promptly disappears If intestinal obstruction is the primary cause of the tetany it must be alleviated

Treatment —Treatment of tetany depends upon its cause Acid producing salts however are good for all forms of tetany Aqueous solutions of ammonium chloride or calcium chloride in 1 Gm doses up to 6 or 8 Gm a day are beneficial whether the tetany is due to low blood calcium or alkalosis Hydrochloric acid may also be used Milk is also highly desirable as a basis for

food because of its high calcium and phosphorus content

Specific therapy for tetanies associated with a low blood calcium is as follows slow intravenous injection of calcium chloride (10–20 cc of a sterile 5 per cent solution) or calcium gluconate (10 cc of a 20 per cent solution) Only the latter solution may be given intramuscularly This therapy gives almost immediate but transient relief though the injection may be repeated after an hour

More permanent effects can be obtained by the following methods

1 The parathyroid hormone may be given intramuscularly (up to 500 units daily) Its effect begins four hours after injection and lasts twenty hours Continued dosage must be controlled by repeated determination of the blood calcium level for overdosage will result in dangerous hypercalcemia This agent has the disadvantage of losing its influence after several months of use and therefore is better kept in reserve for emergencies

2 High vitamin D ingestion which can now be given as irradiated ergosterol in amounts five to ten times the usual antirachitic doses By this means calcium absorption from the intestines is improved and calcium is also liberated from the bones This effect is obtained only after several days This treatment is of value in all tetanies with low blood calcium particularly in cases of steatorrhea Highly irradiated ergosterol, such as dihydroxytachysterol, increases calcium absorption from the intestines and mimics the action of parathyroid hormone in raising the blood calcium level No immunity to it appears to develop It is, therefore a drug of great value in the treatment of tetany Its effects last for several weeks so that overdosage is undesirable Repeated blood calcium determinations are essential in the first few weeks of its use in order to establish the proper dosage

ANALYTICAL FINDINGS IN VARIOUS TETANIES AND RELATED DISORDERS

DISEASE	BLOOD PLASMA VALUES				EXCRETION DURING LOW CALCIUM DIET			
					URINE		FECES	
	CALCIUM	PHOSPHORUS	pH	PHOSPHATASE	CA	P	CA	P
Tetany due to parathyroid deficiency	low	high	normal	normal	low	low	normal	normal
Hyperparathyroidism	high	low	normal	high	high	high	normal	normal
Steatorrhea—difficulty in absorbing calcium from the intestines	normal or low	low	normal	normal or slightly high	low	high	high	normal
Osteomalacia from deficiencies and rickets	normal or low	low	normal	high	low	low	low	low
Hyperthyroidism	normal	normal	normal	high	very high	very high	high	high
Paget's disease (osteitis deformans)	normal	normal	normal	very high	No marked abnormality			
Gastric tetany	normal	normal	increased					
Hyperventilation	normal	normal	increased					
Excessive bicarbonate ingestion	normal	normal	increased					

3 Thyroid extract increases the calcium exchange and is of considerable value in elevating the blood calcium in tetany

4 *A high calcium intake best obtained* through milk and calcium lactate or gluconate (10–12 Gm a day) is essential High protein diets should be avoided

5 For tetanies caused by alkalosis the treatment consists of eliminating the cause and correcting the alkalosis by the ingestion of therapeutic doses of hydrochloric acid ammonium chloride or acid phosphates Sodium chloride in large amounts of fluid may be used if the kidney function is adequate to retain the acid radicle

JOSEPH C AUB

HYPERPARATHYROIDISM

(Osteitis Fibrosa Cystica)

From our present knowledge, it is obvious that a definite abnormality of calcium and phosphorus metabolism must be established before a diagnosis of parathyroid disease can be made Since the original observation of Mandl, the clinical condition of generalized osteitis fibrosa cystica of von Recklinghausen is recognized as due to adenoma or hyperplasia of the parathyroid glands

Symptoms and Signs—Hyperparathyroidism is characterized by

1 Thinning of the skeleton but not the teeth frequently with multiple bone cysts



Fig 165—X ray of the femur showing the rarefaction and expansion of the bone with coarse trabeculation characteristic of osteitis fibrosa cystica

so that spontaneous fractures may occur Great milk drinkers do not show this thinning as the heavy demands for calcium are obtained from the food

2 Increase of bone osteoclasts with the formation of giant cell bone tumors and epulis about the teeth

3 Muscular weakness hypotonia lack of appetite nausea constipation and pain in the bones Polyuria is usually present

4 Renal stones are fairly common in the disease because of the high urinary calcium excretion Unexplained and particularly recurrent stones are reasons for suspecting hyperparathyroidism and looking for a high blood calcium Chronic nephritis develops in the more chronic cases a nephritis produced by the body s own secretions

5 The laboratory findings which are essential to establish the diagnosis, are shown in the Table (see page 1249) In severe cases, when the blood calcium is above 15 mg per cent, the blood phosphorus also rises above normal

6 The increased viscosity of the blood which is seen in experimental hyperparathyroidism is usually not seen in clinical cases

7 Because of great fibrosis in the bone marrow an occasional case of anemia and leukopenia may be encountered

Pathology—The enlarged parathyroid glands are either adenomatous or hyperplastic in appearance They can be palpated only rarely before operation because of their small size and soft consistency and because they are molded into crevices The gross diagnosis is made by their position and salmon or yellow color

Adenomas are usually single but have occasionally been found in more than one gland Chief cells are always present in these tumors though oxyphil or wasserhelle cells may also be present in high proportions In hyperplasia the parathyroids are all enlarged because of generalized wasserhelle cell proliferation The differential diagnosis must be made at operation

The bones show decalcification with a great increase of osteoclasts osteoblasts and fibrous tissue As a result of these cellular changes there may be found osteoclastomas and also multiple cysts with fibrous walls

Prognosis—When the disease is discovered early and the tumor removed prognosis is excellent for marked recovery The giant cell tumors tend to disappear the bone cysts fill in slowly and the bones become heavier The bone pains and general lassitude promptly disappear There is a prompt and marked increase in appetite and a definite reduction in polydipsia and polyuria The grave postoperative risk lies in the appearance of tetany which is more apt to occur in cases with severe bone decalcification If the tumor is not removed the disease progresses The bones become so thin

that there are spontaneous fractures and collapse of the vertebrae the patients become bedridden and die with a renal insufficiency

Treatment —Surgical removal of the enlarged parathyroid tissue is indicated It is preferable to visualize all glands This is *especially important when hyperplasia* is indicated by frozen section, for then a subtotal parathyroidectomy should be done After removal, the blood calcium and phosphorus levels return toward normal The correction may be too great so that tetany may appear A marked storage of calcium *and phosphorus in the bones* follows the operation and this continues for many months The blood phosphatase level returns to normal only after some months

A diet with adequate vitamin D and very high in calcium and phosphorus should be maintained for many months

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DISEASES OF THE PINEAL GLAND

SINCE the turn of the present century the number of investigations concerning the pineal gland has increased steadily but the function of this small structure remains a source of speculation as was true when Descartes believed it to be the seat of the soul The anatomy of the pineal is fairly well agreed upon by most contemporary investigators but there is still a wide divergence of opinion concerning its physiologic significance

Anatomy.—The pineal gland (epiphysis conarium) is a small firm body, approximately 7 by 4 mm in size in the adult It lies at the posterior and superior extremity of the third cerebral ventricle between the splenium of the corpus callosum and the corpora quadrigemina In some of the lower vertebrates it is a parietal organ with the structure of a primitive eye but it is present in all mammals as a separate and internal organ a part of the brain, with a constant location at the posterior border of the roof of the third ventricle In the human embryo the pineal *anlagen* appear at the second month as folds in the diencephalic roof and there is a continuous metamorphosis of the organ until its more or less definitive form is attained at one year after birth Microscopically the pineal gland consists of characteristic parenchymal cells varying amounts of neurologic substance a few nervous elements and blood vessels Seldom before puberty but frequently after adolescence calcium salts may be deposited in the gland

Physiology —Most of the present-day disagreements on the physiology of the pineal concern the secretory potentialities of the parenchymal cells Of all investigations to date Tilney's work was painstakingly done and is classic On the basis of comparative anatomy and histologic structure he unequivocally placed the organ among the true glands with the likelihood of its having an actual endocrinal function Based upon anatomic experimental (extract feeding extirpation transplantation) and clinical observations Krabbe Hortega Horrax Foa Izawa McCord *and many others* also believe the pineal body to be essentially a glandular structure with corresponding function and purpose in the organism Directly opposed interpretations may be found in the opinions of Dandy Bailey and other investigators

Extirpation of the gland in young animals

transplantation experiments electrical stimulation of the organ feeding pineal substance or extract to immature animals, clinical studies of patients suffering from pineal tumors and the therapeutic effects of the administration of pineal extracts to patients have been the various investigative methods employed As is true in the attempts to determine the function of other glands belonging to the endocrine group feeding experiments in the laboratory or clinic have been followed by many uncritical and worthless reports in the literature

As a result of these experiments the epiphysis thus far has been assigned many roles a stimulator of sexual growth, an inhibitor of sexual growth a rudimentary third eye carried over from the reptile stage a true endocrine gland and a nonglandular structure with regressive characteristics as the phyla ascend and with no function whatever With the preponderant evidence available at the present time it cannot be denied that the pineal body is developmentally and structurally a gland with potentialities of glandular function What the effect of the pineal secretion (assuming its existence) may be alone or in conjunction with the other endocrine glands has not as yet been discovered

Recently Davis and Martin extirpated the pineal gland in young rats cats and dogs Adequate litter mate controls of each sex were used for comparison of their development No behavior changes were noted in the pinealectomized rats and sexual maturity was attained at the same age in both control and lesion animals There was some indication of an increased somatic development in the male rats at puberty There was no somatic or sexual maturation differences in the female control and pinealectomized cats Both experienced normal estrus and both conceived normal pregnancies but their offspring sired by pinealectomized males were weak The pinealectomized mothers showed a lack of maternal instinct and lactated inadequately The pinealectomized males matured sexually four to five months earlier than their controls and they showed a precocious somatic development being still larger than their controls at the time of full maturity of the normal cats No significant differences were noted in the histologic picture of the thyroid, adrenal glands, or ovaries between the mature control and lesion animals The testes and hypophyses of the pinealectomized males were larger than those of the control males and the histologic picture of these organs reflected the gross appearance

Symptomatology—It has been noted repeatedly in reviews of the histories of patients with pinealomas pineoblastomas or teratomas of the pineal gland that the great preponderance of the patients are of the male sex A high percentage of these individuals are found to have developed their symptoms prepubertally, and of these many show the syndrome of precocious puberty (Pellizzi syndrome, macrogenitosomia praecox) Such patients may show signs of premature development as early as eighteen months of age and many cases are reported in children with pineal tumors who as young as five years have grown to an unusually large stature with adult body configuration and hair distribution and with genitalia of adult size Signs of sexual function such as erections emissions masturbation, and interest in members of the opposite sex often accompany such evidence of premature somatic and sexual maturation It is extremely rare for tumors of the pineal gland to hasten the advent of puberty in females in all but a few rare cases the syndrome has been limited to boys This is entirely in keeping with most of the results of the experimental removal of the gland in young animals sexual and somatic overgrowth being produced in males but rarely or irregularly so in females Pineal tumors occurring past the age of puberty have been found to occur in males in 75 per cent of the cases in what is the largest collection of such tumors in this country * so that it becomes a matter of particular interest that all ages considered pineal tumors occur preponderantly in the male sex Of course pineal tumors occurring after puberty do not involve the question of the role of the pineal gland in the sexual and somatic growth of the individual

While not every prepubertal patient with a pineal tumor shows the signs of precocious puberty practically every patient with such

* Brain Tumor Registry Yale University Medical School

a tumor does present a more or less uniform set of symptoms such as would be expected to follow the presence of any expanding lesion in the location of the pineal gland Almost invariably there is a marked and progressive internal hydrocephalus because of the interference by the tumor with the circulation of the cerebrospinal fluid through the aqueduct of Sylvius In the preterminal state due to the increasing intracranial pressure headache (sometimes frontal but most frequently suboccipital) suboccipital tenderness neck rigidity vomiting and weakness are among the most outstanding signs With the continued effects of the increased pressure and invasion by the tumor of the surrounding brain the patient suffers progressive loss of vision due to destruction of the optic chiasm and tracts or quadrigeminal plate or both various paralyses of the extra-ocular muscles deafness loss of weight increasing stupor and slowness of cerebration convulsions and finally coma with death Due either to implantation of pineal tumor nodules in the floor and walls of the dilated third ventricle and infundibulum or due to pressure effects in the pituitary gland and its stalk it is very frequently true that for the last few months of life these patients may develop a severe diabetes insipidus consuming as much as 5 to 6 gallons of water daily

Other secondary pituitary and hypothalamic signs may arise as well There may be blotchy pigmentation of the skin a subnormal body temperature bradycardia very low blood pressure increasingly long periods of somnolence and marked cachexia Frequently those children who are precocious both mentally and physically early in the disease become very dull and show peculiar behavior patterns several weeks before death Adults may suffer sexual debility Amenorrhea is a common symptom in females Some children with pineal tumors may show signs within the first year or two of life of premature development yet may live for several years with no signs of the disease other than those referable to this precocious growth Indeed such a patient may not die until much later when the tumor has grown to sufficient proportions to produce the terminal symptoms mentioned so that though his disturbance may have been originally due entirely to pineal disease, it may later become confused with symptoms of hypothalamic and pituitary disease as well

Treatment—It was Marburg who first popularized the conception that the pineal gland delays and inhibits the onset of sexual maturation and that in the absence of its inhibitory hormone due to removal or destruction by a tumor the body is free to proceed rapidly to puberty Many case history reports (Horrax Timme and others) lend support to this idea but other accounts are correspondingly contradictory from both the clinical and experimental standpoints In line with the suggestions of Marburg and Timme the feeding of pineal substance has been empirically used for clinical purposes in cases of pineal deficiency in the past two decades Recently it has again become a popular but not scientifically accepted therapeutic agent in certain clinics Before there is actual evidence of increased intracranial pressure from a tumor or when only functional signs of pineal insufficiency are present glandular extract or substance may be used hopefully

A tumor of the pineal gland is definitely a surgical problem Because of its location and the usual poor condition of the patient when surgery is accepted complete removal is difficult and frequently impossible Many successful removals of pineal tumors have been reported and with the constant progress in neurologic surgery improved results in the future may be expected

The physiology of the pineal gland remains an unsolved problem and therefore the significance of its pathologic state before the appearance of signs of a space occupying tumor is but poorly understood Whether it is a true endocrine gland with a secretion of its own what its relationship to other glands of internal secretion is and what the functional implications of its peculiar histologic anatomy may be are still matters of investigation Only further and more conclusive research will prove whether it is to be classified eventually in hormonic relationship to the other endocrine glands—gonads hypophysis adrenals thymus and thyroid

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DISEASES OF THE SEX GLANDS

DISEASES OF THE MALE GONADS

EMBRYOLOGY

The undifferentiated sex gland develops about the fifth week from the medial surface of the mesonephros Differentiation into testis or ovary occurs during the sixth or seventh week Whether a male or female will develop seems to depend upon the type of spermatozoon with which the egg is fertilized, those with the so called Y chromosome giving rise to males In some instances *gonadal* tissue of both sexes may appear in the same individuals It may occur unilaterally or bilaterally and give rise to a true hermaphrodite *i e* an individual with the internal and external genitalia of both sexes True hermaphroditism is very rare and is *not* to be confused with pseudohermaphroditism, in which the individual is born with the gonads of one sex but has the secondary sex characteristics of the opposite sex Testicular tissue may appear in virilizing arrhenoblastomas of the ovary The Wolffian and Mullerian structures both appear in each individual possibly as relics of very early vertebrate life when all individuals produced both sperm and eggs If a testis develops, the Wolffian body and duct give rise to a vas deferens seminal vesicles epididymis and ejaculatory duct At the same time the Mullerian structure atrophies but vestiges remain (appendix testis and utriculus masculinus) From the urogenital sinus and genital tubercle there develop a prostate gland Cowper s glands a male type of urethra a scrotum and a penis If an ovary develops the Mullerian ducts give rise to oviducts, uterus and upper vagina while the Wolffian structures atrophy The urogenital sinus and genital tubercle develop into the lower vagina female urethra Bartholin s glands and external female genitalia According to Ivy Greene and Burrill the differentiation of the external genitalia takes place a little later than that of the internal and abnormal hormone stimulation may result in their assuming the characteristics of the opposite sex In this way they believe the development of pseudohermaphroditism may be explained It follows that every individual is in a sense bisexual throughout life One sex usually predominates but vestigial organs of the opposite sex remain and their development may be stimulated by sex hormones Ivy *et al* have shown that if this stimulation is applied sufficiently early in embryonic life all sorts of interesting bisexual developments may result

Many details of descent of the testis are still to be worked out The consensus among embryologists is that the cells of the proximal portion of the genital mass atrophy while those of the distal portion proliferate

at the same time the fetus grows so that the testis appears to descend to the level of the inguinal ring which is being prepared for it By the fourth month, the testis lies just inside the internal inguinal ring by the seventh month at the lower end of the canal and during the last month of intra uterine life it descends into the scrotum The pouch of peritoneum which later be comes the tunica vaginalis precedes the testis into the scrotum The gubernaculum is sup posed to play an important role in directing the course of descent It is attached very early to the genital ridge as it develops downward and in the beginning has attach ments to the abdominal muscles the root of the penis Scarpa s triangle the base of the scrotum and the perineum

ANATOMY AND PHYSIOLOGY

The testis consists essentially of two parts (1) the seminiferous tubules which produce spermatozoa and (2) the inter stitial cells which produce male sex hormone (Fig 160) What relationship if any exist between these two structures is unknown The production of the male sex hormone results in the development of secondary sex characteristics namely change in pitch of voice the growth of the penis scrotum pros tate seminal vesicles epididymis vas de ferens body hair, beard and to some extent skeletal growth including contour of the body A delicate balance exists between the anterior lobe of the pituitary and the gonads the best example of which is seen in the menstrual cycle in the female The pituitary stimulates the activity of the gonads and the production of sex hormones by them may serve as a check on the pituitary itself The factor or factors responsible for the in itiation of the pituitary stimulus are not clearly understood There is some evidence that there may be two gonadotropic prin ciples corresponding to two gonadotropic ef fects of the anterior lobe of the pituitary One causes development of the follicles of the ovary and influences the function of the seminiferous tubules in the testis (the so called follicle stimulating hormone) and the other causes luteinization of the follicles in the ovary and influences the activity of the interstitial cells in the testis (the so called luteinizing hormone) Menopausal and castrate urines contain primarily the follicle stimulating material while human pregnancy urine contains largely the lutein izing factor which is available under a va riety of trade names (Korotrin Follutein, A P L Antuitrin S Pranturon, etc) Gonadotropic material from the serum of the pregnant mare (Gonadogen, Anteron, etc) and commercial preparations from the pituitary itself contain both factors It is thus theoretically possible to stimulate the testis selectively although in actual practice the gonadotropic material from human preg nancy urine (chorionic gonadotropin) is the only one with which adequate stimulation

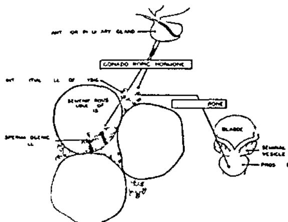


Fig 160—Diagram showing the action of gonadotropic factors of the anterior pituitary on the testis. The gonadotropic hormone stimulates the testis, causing it to secrete male hormone which maintains the secretory activity of the accessory glands (From Engle, E T Male Reproductive System in Cowdry s Problems of Ageing Williams & Wilkins Co Baltimore, 1939)

of the testis has been produced up to the present time The material from the serum of the pregnant mare produces only slight stimulation in the doses commonly used Pituitary preparations are not of much value at present and the material from meno pausal and castrate urines is not available in sufficiently large quantities

The form in which the male sex hormone is secreted by the testis is unknown The most active substance isolated so far is testosterone which is six times as potent as androsterone the first androgenic material isolated from urine Some esters of testos terone are more potent than testosterone

itself and in clinical work the propionic acid ester (testosterone propionate) is used *Trade* names for this product are Oreton Perandren and Neo Hombreol For therapeutic purposes testosterone is made synthetically Twenty nine related compounds (including androsterone and dehydroandrosterone which have been isolated from urine) *have also been prepared synthetically* by the degradation of sterols but they are not used therapeutically *In July 1935* the League of Nations Committee decided that one international unit of male sex hormone would be *100* micrograms of crystalline androsterone

Very little androgenic material has been recovered from the urine of young boys and girls from six to ten years of age—only from 0 7 to 2 0 international units per liter A marked increase in the amount found in urine begins at about the time of puberty the urine of an adult male containing about 40 to 100 international units in twenty four hours The amount secreted appears to diminish with advancing years but accurate data are not available The production of spermatozoa also appears to diminish in later *life but the change is variable, and* again accurate data are not available What role if any sex hormones play in embryonic development has not been established but they may be responsible for the develop *ment of secondary sex characteristics*

For some reason not clearly understood estrogenic material is found in male urine (the equivalent of 10 micrograms of theelin per day) and female urine is just as rich a source of male hormone as male urine and contains from 30 to 100 international units in twenty four hours Koch has pointed out that human *urine is almost unique in* its androgenic content the urine of the stallion bull ram and rat containing very little

W O Thompson

PUBERTY IN THE MALE

Following the disappearance of prenatal enlargement and engorgement the genitalia remain relatively stationary in size until the eleventh to the thirteenth year when the changes of puberty begin to appear in association with a *marked* increase in the excretion of androgenic material in the urine What role, *if any* the gonads play in somatic development from birth to puberty is un*known* During puberty the external genitalia *gradually increase in size, the skeleton grows rapidly* and the emotional changes associated *with the* increase in sexual function appear The prostate which is usually *not palpable in young boys begins to* develop reaching its adult size at about the same time as the external genitalia Hair begins to appear on various *parts of the body* The pubic hair at first is usually feminine in distribution but after a period of several *months* fine short hairs begin to appear in the lower midline of the abdomen and then often all over the abdomen chest back arms and legs However the amount of body hair is very variable many apparently normal men having very little and exhibiting an almost feminine distribution of pubic hair The beard appears as a fine fuzz and *then gradually increases in length and stiff*ness The pitch of the voice gradually becomes lower Marked alterations in body contour may take place The amount of fat in the abdomen and thighs may diminish *and the shoulders become broader* The relation between the length of the trunk and the length of the extremities is affected absence of testicular function during the age of normal puberty resulting in long extremities and a comparatively short trunk Skeletal growth may at first be stimulated but epiphyseal union is nearly complete about the end of the *pubertal period* In men this usually occurs during the sixteenth or seventeenth year and in women between the fourteenth and sixteenth years *The* epiphyses of the vertebrae pelvis and clavicles do not unite until a little later In man and lower animals spermatogenesis occurs at a somewhat later time than the corresponding first *menstruation or* first estrus Familial instances of puberty occurring prematurely at the age of five to nine years are described although the condition is rare In a similar manner the onset of puberty may be greatly delayed although this disturbance usually indicates a deficiency of pituitary function

While the changes of puberty depend upon the production of male sex *hormone* the stimulus for the increased activity of the

testis is provided by gonadotropic material from the anterior lobe of the pituitary It is not definitely established why puberty occurs when it does According to Engle the seminiferous tubules in the testis and the follicles in the ovary can respond to gonad activators only after the gonads have undergone a certain amount of ripening which may be independent of the hypophysis In the age of puberty suggests that the pituitary stimulus itself may be held in abeyance.

W O THOMPSON

PRECOCIOUS SEXUAL DEVELOPMENT

In the course of treating young boys for undescended testes with chorionic gonadotropin striking genital growth may be observed The changes may be so marked that

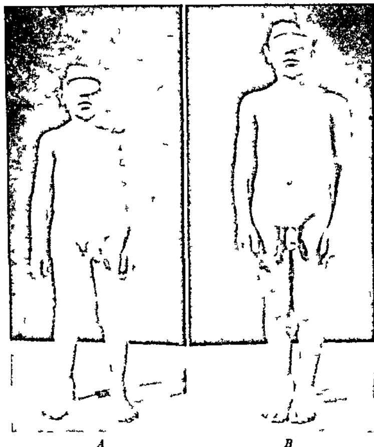


Fig 167—Precocious sexual development and rapid skeletal growth during treatment with chorionic gonadtropin

A July 18 1936 before treatment, age six years seven months Weight 19.5 kg (43 pounds) Ht. 114 8 cm (44¾ inches)

B July 24 1937 after eleven and one-half months of treatment with follutein (total dose 56.5 0 rat units) Weight 27.8 kg (61¼ pounds) Ht 128 0 cm (50 inches) (Thompson and Heckel, J.A.M.A., *110* 1813, 1938)

the case of the interstitial cells of the testis this conclusion does not appear to apply They may be stimulated to increased activity at any age before puberty by gonadotropic material from human pregnancy urine and a condition simulating premature puberty produced (see section on Precocious Sexual Development) The fact that these changes do not occur normally until

a condition resembling premature puberty is produced This phenomenon is illustrated in the accompanying photographs of a six and one half year old boy who was treated for a right undescended testis and an inguinal hernia In the course of a few months his penis became larger than that of his father There was an increase in the size of the scrotum and prostate a growth of pubic hair a

marked increase in the frequency of erections a change in the pitch of the voice and some growth of hair on the sides of the face although a true beard did not develop His height increased rapidly The testes increased little if any in size during treatment, presumably because this material stimulates *primarily the interstitial cells* and not the seminiferous tubules The right testis descended but remained smaller than the left and the associated hernia did not disappear but became strangulated and had to be corrected by operation No change was noted in basal metabolism during treatment

When treatment was discontinued some regression in size occurred The penis became slightly smaller and much less engorged but remained much larger than before treatment was started The prostate became flat and much smaller in diameter and the body weight and height which had increased more rapidly than normal during treatment increased only very slowly for the next two and one half years The pubic hair decreased to about one third of its maximum amount but did not disappear completely Whether or not this treatment will result in premature closure of his epiphyses is unknown Precocious sexual development associated with interstitial cell tumors of the testis is said to stimulate skeletal growth at first but ultimately to cause the individual to become shorter than he might otherwise have been because of premature epiphyseal union If treatment with chorionic gonadotropin is carried out for a sufficiently long period young boys may sometimes be made very large for their age but the final height does not appear to be altered unless pituitary dwarfism is present

The susceptibility to this growth stimulus varies markedly but it appears probable that precocious genital growth may be produced with it in most normal young boys if sufficiently large doses are used Premature sexual development is also said to be produced in man by tumors of the adrenal cortex and pineal gland and occasionally by tumors of the testis and lesions of the mid brain Its relation to pituitary disturbances is open to question There are cases which can be explained only by a marked familial tendency to precocious development In animals thymus extracts are reported to be powerful sex stimulants It would be desirable to know whether the mechanism involved in the production of premature sexual development in these pathologic conditions is similar to the mechanism involved in its production from the administration of chorionic gonadotropin The association of premature puberty with interstitial cell tumors of the testis is of interest in view of the fact that chorionic gonadotropin is known to stimulate the interstitial cells It is also of interest that, in patients showing precocious development of the genitalia associated with tumors of the adrenal cortex, the testis shows little or no increase in size and spermatogenesis may not occur

W O THOMPSON

HYPERGONADISM AND HYPOGONADISM

As in the case of other glands of internal secretion the testis may theoretically show various degrees of hyperfunction and hypofunction States of hyperfunction associated with increased production of male sex hormone undoubtedly occur but are not clearly defined It is difficult to differentiate the effects of overproduction of sex hormone from those of overactivity of the sympathetic nervous system For the most part disorders of function requiring treatment are those associated with hypofunction of the testis In most instances both portions of the testis are affected

PRIMARY AND SECONDARY HYPOGONADISM

The testis, like the ovary may fail to function properly because of some defect inherent in the testis itself (primary hypogonadism) or because of lack of adequate stimulation notably by the anterior lobe of the pituitary (secondary hypogonadism) As in the case of the thyroid normal pituitary function is necessary for normal testicular function and in its absence atrophy of the testes and genitalia occurs, with decrease in or disappearance of spermatogenesis and production of male sex hormone Secondary hypogonadism appears to be more common than the primary type although there is some question at present

as to just how some disorders should be classified Cases of undescended testes in which descent is prevented by mechanical factors and cases in which the testes are removed or destroyed by various agents represent examples of the primary type, while all cases associated with hypopituitarism and cases of undescended testes in which descent is prevented by some hormonal deficiency appear to be of the secondary type

W O THOMPSON

TYPES OF THERAPY IN HYPOGONADISM

Two types of therapy are now possible in hypofunction of the testis (1) substitution therapy with male sex hormone and (2) stimulation therapy with gonadotropic material In substitution therapy the male sex hormone which the testis is not capable of producing in sufficient quantity when stimulated is supplied artificially Examples of conditions in which it is indicated are eunuchism and most cases of eunuchoidism The male sex hormone has also been reported to produce improvement in patients with benign prostatic hypertrophy and to rejuvenate old men It appears to alter the function of the normal testis as judged by a decrease in spermatogenesis during its administration and should be used only in those instances in which the testis is incapable of responding to stimulation With gonadotropic material the testis is stimulated to increased activity so that the testis itself produces more male sex hormone and it is to be preferred in most instances in which the testis is capable of responding to stimulation Examples of conditions in which stimulation is indicated are undescended testes and hypopituitarism with secondary hypogonadism including the Frohlich syndrome

CONDITIONS IN WHICH SUBSTITUTION THERAPY IS INDICATED

Eunuchism — *Definition* — Eunuchism represents complete loss of testicular function from castration inflammation or mechanical injury

Pathologic Physiology —The basal metabolism often shows a moderate depression but is usually not lower than minus 20 to minus 25 per cent The urine shows a marked decrease in its content of androgenic material

Symptoms —The symptoms depend to some extent upon whether the condition develops before or after puberty the chief difference being the effect on body contour The effect of loss of function on skeletal development does not show up until about the time of puberty, when the extremities become very long in proportion to the comparatively short trunk the voice remains high pitched and the secondary sex characteristics fail to develop The individuals affected are usually tall and have a narrow chest and shoulders They are usually very shy effeminate and high strung Pubic and axillary hair fail to develop there is no growth of beard and no development of hair on the chest abdomen arms or legs The genitalia remain infantile The prostate is usually not palpable The muscles are small and feminine in type There may or may not be slight development of breast tissue but it is much less marked than in individuals of the Frohlich type Obesity may be an associated phenomenon but it often is not present In fact the patients may weigh less than normal in contrast to the condition presented by patients of the Frohlich type who may be excessively fat When testicular function is lost after normal masculine development has taken place the skeleton is not affected and many of the secondary sex characteristics tend to persist The penis and scrotum become slightly smaller but remain nearly as large as before loss of function the prostate usually atrophies the growth of hair on the face, pubes axillae and other regions may decrease markedly but usually does not disappear completely The pitch of the voice may become slightly higher but usually retains much of its masculine quality There is decrease in sexual desire but ability to perform the sexual act is often not completely lost There is a marked decrease in bodily vigor and muscle strength decrease in ambition and the development of a somewhat placid and listless individual There are sometimes nervous phenomena resembling those of the climacteric in women

Eunuchoidism —*Definition* —Eunuchoidism is the term applied to partial loss of testicular function The decrease in func

tion may vary from a slight deficiency to almost complete loss The eunuchoid state may result from a primary defect in the testes themselves or from inadequate stimulation of the testes by the anterior lobe of the pituitary

Pathologic Physiology —Moore has pointed out that the testes can develop normally only in the environment of the scrotum When they are deflected over the external oblique they appear to function better than when they remain in the abdominal cavity When both testes fail to descend both testes in the scrotum The testes are usually small and show varying degrees of function

Symptoms —When the secondary sex characteristics develop normally the body contour is usually normal even though both testes remain within the abdomen, and when the secondary sex characteristics do not develop, the skeleton seems to assume the typical eunuchoid character (Fig 168) These facts indicate that the male sex hormone is necessary for normal skeletal growth Other functions of this hormone in



Fig 168 —Eunuchoidism (bilateral intra abdominal cryptorchidism) in a man aged twenty nine showing no effect from treatment with chorionic gonadotropin and a marked effect with testost rone propionate

A July 22 1937 before treatment Patient had extremely small genitalia and the prostate was not palpable He was effeminate smooth skinned had no beard and no hair on his abdomen or extremities There was a small amount of pubic hair His voice was high pitched and he had a marked inferiority complex

B February 25 1933 after 1 024 000 rats units of A P L Practically no change in genitalia Prostate not palpable He had gained 2½ kg Contrast this lack of effect with the marked effect of A P L in Fig 172

C September 26 1939 after 8800 mg of Oreton Marked growth of genitalia Prostate 3 cm in diameter Increased growth of hair on body and development of a more normal body contour in spite of a gain of 9 0 kg The patient grew a beard requiring him to shave every other day His voice became masculine and he became much more energetic and aggressive

from the abdominal cavity virtually complete lack of testicular function often results However evidence of feeble attempts at function are often noted in the appearance of a few pubic hairs and the condition is probably best referred to as eunuchoid in type The interstitial cells are apparently less susceptible to damage from the environment of the abdominal cavity and may show almost normal function even though both testes remain in the abdomen Between these two extremes all variations are possible Eunuchoidism may also be present with the body are illustrated by its effect in patients showing complete loss of function

TREATMENT OF EUNUCHISM AND EUNUCHOIDISM

Substitution therapy is required in all cases of eunuchism and most cases of eunuchoidism because of inability of the testis to respond to stimulation Large doses of testosterone propionate are indicated (25 0 mg daily) The doses originally recommended (from 1 to 5 mg daily) are in

adequate The compound methyl testosterone produces some effect by mouth but it is better in all eunuch and eunuchoid individuals to give testosterone propionate parenterally, at least until maximum changes have been produced In order to simulate natural phenomena and to prevent the development of the skeletal characteristics of the eunuchoid state it is probably desirable in all castrates and in all patients with bilateral intra abdominal cryptorchidism to begin treatment just before the age of normal puberty namely at about the age of eleven years When this is not done and the typical eunuch or eunuchoid changes have been allowed to develop Thompson and Heckel have demonstrated the following effects with large doses of testosterone propionate

1 The gradual appearance of the secondary sex characteristics of the adult male (Fig 168) The infantile penis may become normal in size the prostate develops and hair grows in the pubic and axillary regions on the face and on other parts of the body The pitch of the voice rapidly assumes its characteristic masculine quality Erections and seminal emissions become very frequent Priapism has been described

2 A marked increase in appetite and body weight (as much as 40 pounds [18 Kg] in four months) The patients do not become obese but show an enormous increase in the size firmness and strength of muscles The material appears to stimulate development of the muscular characteristics of the normal male whereas in the eunuchoid state the muscle development resembles that of the female This change is very dramatic

3 An increase in basal metabolism of as much as 30 points

4 An increase in vigor and sense of well being The patients are capable of and have the initiative to do much more work both mental and physical They seek and become much more proficient in games involving muscle coordination and physical stamina

5 Loss of their effeminate characteristics Whereas before treatment they tend to run away from arguments and physical combat after treatment they tend to welcome opportunities to demonstrate their physical prowess

A typical example of what may be accomplished with this treatment is illustrated in Figure 168 As in all conditions involving substitution the response is determined not only by the substance employed but also by the susceptibility of the organ involved There are thus variations in the amount of growth of the penis that may be produced with this material and development usually stops before the size becomes completely normal Observations appear to indicate that the rate at which development of secondary sex characteristics can be induced cannot be accelerated beyond a certain point This is not surprising in view of the fact that the changes associated with normal puberty occur gradually over a period of several years The details of treatment in eunuch and eunuchoid individuals are still to be worked out When there is complete lack of sex development it is probably necessary to give intensive treatment for between one and two years and then continue with maintenance therapy for the rest of the patient s life In individuals whose testicular function disappears after normal development has taken place a shorter period of intensive therapy may be necessary What the maintenance dose will prove to be in both conditions is still to be determined (possibly 25 0 mg once or twice weekly)

The doses of testosterone propionate recorded refer to the preparation in oil for subcutaneous or intramuscular injection The compound is relatively insoluble in body fluids and may therefore be implanted subcutaneously in the form of pellets just as desoxycorticosterone has been in the treatment of Addison s disease It is still to be determined however whether enough absorption for adequate therapy will occur from pellets

OTHER APPLICATIONS OF SUBSTITUTION THERAPY

The Male Climacteric —A condition has been described in some males resembling the female climacteric and characterized by vasomotor and emotional instability The condition is not common and there is no definite period of loss of sexual function in the male like the menopause in the female More than 50 per cent of men over seventy

years of age are reported to show spermatozoa Nevertheless the meager observations that are available on spermatozoa counts and excretion of androgenic and gonadotropic material in the urine suggest that some waning of sexual activity occurs with advancing years, the age of onset varying tremendously from individual to individual Brown Sequard and others have associated the fatigue and decreased vitality of advancing age with decrease in sexual vigor However, the problem of aging is a complex one and probably involves all glands of internal secretion and the tissues which they stimulate While there probably is in some men a true climacteric which is relieved by the administration of testosterone propionate the characteristics of this disorder and the details of its treatment are still to be worked out

Impotence—The most important point in the management of impotence is to determine its cause Many cases are psychogenic in origin and the promiscuous use of glandular therapy is to be deplored When impotence is associated with a gradual decline in sexual function with advancing years or when the onset is associated with injury to the testes or with atrophy secondary to hypopituitarism then some improvement may be expected from glandular therapy This may be of the substitution or stimulation variety depending upon the capacity of the testes to respond

Sterility—In sterility the spermatozoa may be absent greatly decreased in numbers or deficient in quality It may be produced by obstruction to the discharge of spermatozoa or by hypofunction of the seminiferous tubules Testosterone propionate depresses rather than stimulates the function of the testis and has no place in the treatment of this condition Heckel has been able to depress the number of spermatozoa in men with normal counts almost to the point of azoospermia by the administration of testosterone propionate the count returning to normal some time after treatment was discontinued In other words it would appear that testosterone propionate produces at least a temporary injury to the seminiferous tubules of the normal testis and its use is contraindicated in most patients in whom the testes are capable of producing spermatozoa Sterility presents a complicated problem and its treatment at present is unsatisfactory In some instances deficiencies in quantity and quality of spermatozoa appear to be related to deficiencies in the function of the anterior lobe of the pituitary Some improvement in therapy may be expected from the development of a more potent gonadotropic factor from the pituitary The gonadotropic material from the serum of the pregnant mare should theoretically be of value because it contains material which stimulates the seminiferous tubules but in actual practice it is not very effective Chorionic gonadotropin does not represent adequate therapy because it stimulates primarily the interstitial cells

Benign Prostatic Hypertrophy—In contrast to the numerous reports of beneficial results from the use of male sex hormone in benign prostatic hypertrophy, the experience of Heckel and Thompson with this material in such cases has been disappointing Since the male sex hormone causes development of the prostate in the first place it is not easy to understand how its use in benign prostatic hypertrophy would be beneficial It should also be emphasized that castration causes atrophy and that stimulation of the testes of young animals with gonadotropic principles causes growth of the prostate These facts do not seem to support the hypothesis that testosterone propionate improves benign prostatic hypertrophy

Complications of Treatment with Testosterone Propionate—In young men of the eunuchoid type receiving large doses of testosterone propionate Thompson and Heckel have observed edema of the ankles and marked acne The edema is usually temporary in spite of continued treatment and the younger men usually feel well while it is present One patient complained that palpitation and tachycardia were so marked that he had to discontinue treatment for a short period of time Three old men with prostatic hypertrophy developed edema of the ankles and shortness of breath during treatment K W Thompson has reported the development of generalized puffy edema acne of the face and precordial pain In one of his patients precordial pain was so marked that treatment had to be discontinued In

the younger men the edema may be caused by retention of sodium and other electrolytes while in older men an added factor may be cardiac failure resulting from increased activity It is of interest that desoxycorticosterone which is so closely related chemically to testosterone produces edema of the ankles and occasionally generalized edema in patients with Addison s disease Some retention of water and electrolytes is also noted following the administration of the female sex hormone estradiol Testosterone propionate is a very important therapeutic agent but its use should be restricted to the conditions in which it is indicated and patients receiving it must be followed for long periods of time to determine whether or not there are any untoward late complications

CONDITIONS IN WHICH STIMULATION THERAPY IS INDICATED

Undescended Testes (Cryptorchidism)

—*Definition*—True cryptorchidism is present when it is impossible on repeated examination to displace the testis into the scrotum in any position of the body It is to be distinguished from pseudocryptorchidism in which the testes are migratory and move back and forth spontaneously from the canal to the scrotum The condition is bilateral in from 25 to 40 per cent of the cases The importance of failure of descent of the testis lies in the fact that it cannot function normally except in the environment of the scrotum

Incidence—The highest recorded incidence for adults is 3 1 per 1000 reported by the U S War Department The figures for children appear to be much higher but it is not certain whether or not migratory testes are included in them Drake reports thirty eight cases among 1050 boys from various schools and Williams fifty nine cases among 2104 boys in boarding schools Both observers report descent in about two thirds of the cases during the school age

Pathologic Anatomy—The testis may theoretically be stopped at any point along its so called line of descent In most instances undescended testes are found just inside the internal ring in the inguinal canal or deflected from the external ring in various abnormal positions, usually those in which fibers of the gubernaculum are found early in its development The most common site of abnormal deflection is over the external oblique Undescended testes are occasionally deflected toward the base of the penis and in rare instances in the perineum In some instances intra abdominal testes cannot be found at operation Undescended testes may be associated with actual or potential hernia and sometimes the patient first consults a physician because of strangulated hernia The testis itself is often found to be defective at operation No satisfactory figures are available showing the spermatogenic function of undescended testes after glandular treatment or surgical correction or a combination of both

Pathologic Physiology—The response to treatment in successful cases and the findings at operation in unsuccessful cases indicate that descent of the testis depends upon anatomic integrity of the parts involved and upon hormonal stimulation There is some evidence that increased production of male sex hormone from stimulation of the interstitial cell mass by chorionic gonadotropin may play a role Prenatal hypertrophy and postnatal involution of the interstitial cells of the testis have been demonstrated There is an associated prenatal hypertrophy and engorgement of the genitalia and a postnatal decrease in size The only mammals in which prenatal descent of the testis occurs are those in which chorionic gonadotropin appears in the circulation during pregnancy namely in man and in the great apes In other mammals descent occurs just before or early in puberty but in such animals precocious descent may be induced by administration of gonadotropic material from human pregnancy urine It follows that failure of descent of the testis may be caused by

1 An anatomic deficiency
2 A hormonal deficiency

In other words the condition may be caused by primary or secondary hypogonadism With all the recent work on glandular therapy there has been too much tendency to neglect anatomic defects which appear to play an important role in many cases of undescended testes

Signs and Symptoms —The absence of one or both testes from the scrotum is usually first noted by the child s parents Not infrequently a painful swelling representing an associated inguinal hernia first brings the patient to a physician The effect of deficient testicular function does not become evident until about the time of puberty although some of the boys are rather effeminate The body contour of young boys with undescended testes is usually normal and only occasionally of the Frohlich type When the condition is bilateral and intra abdominal and persists beyond the age of puberty, a eunuchoid condition commonly develops although even the intra abdominal testis may secrete some male sex hormone and preserve normal body contour When the condition is unilateral and persists beyond the age of puberty the scrotal testis usually produces enough male sex hormone to cause normal development of secondary sex characteristics although in some instances the testicular function is deficient and appears to be associated with hypopituitarism The basal metabolism in patients with undescended testes is usually normal but may be moderately depressed In about one third of the cases the condition is associated with other abnormalities among which may be mentioned hypospadias slipping of epiphyses infantile sacrum club feet poorly developed abdominal muscles pilonidal sinus and defective cerebral development

Diagnosis —It is important to distinguish true cryptorchidism from pseudocryptorchidism Migratory testes namely those that move back and forth from the canal to the scrotum are not true undescended testes tend to remain in the scrotum after puberty and therefore require no treatment It is common for the inexperienced observer to consider testes of this type as true undescended testes In distinguishing between true cryptorchidism and pseudo cryptorchidism *it is important that the examiner* have a thorough knowledge of the pathologic anatomy of undescended testes and that the testes be carefully manipulated on more than one occasion with the patient in the upright position The location of an undescended testis cannot be determined accurately with the patient in the recumbent position and a testis cannot be considered intra abdominal unless it is impossible to palpate it by any method of examination A testis which appears to be in the abdominal cavity in the recumbent position is often found in the inguinal canal in the erect position or after straining It should also be pointed out that, in any position of the body it may occasionally be impossible because of retraction to palpate testes that at other times can be palpated Testes which are deflected in abnormal positions notably those over the external oblique can usually be distinguished from those in the inguinal canal by the fact that they lie more superficially and can be moved readily under the skin Those in the upper part of the canal can often be displaced into the abdominal cavity It is important to define the position of the testis accurately because it has an important bearing on the response to glandular treatment

Treatment —The best form of treatment at the present time appears to be the intelligent combination of glandular therapy and surgical procedures In the past few years interest has been aroused in the treatment of undescended testes with the anterior pituitary like principle of human pregnancy urine—also called gonadotropic factor of pregnancy urine or chorionic gonadotropin because of its apparent origin from the chorionic villi in the placenta This material was discovered by Aschheim and Zondek and first tried clinically by Schapiro in young boys with hypogenitalism and undescended testes It is available under a variety of trade names—Korotrin Follutein A P L Pranturon Antuitrin S *etc The preparations* containing 500 and 1000 rat units per cubic centimeter are more practical than weaker concentrations This material stimu*lates the interstitial cells of* the testis to produce male sex hormone This in turn causes enlargement of all parts involved in descent and if pushed too far, precocious sexual development resembling premature puberty (Fig 167)

Hamilton has demonstrated that descent of the testis may be produced by male sex hormone itself but since this may injure the normal testis it is contraindicated unless both testes are within the abdominal cavity Gonadotropic material from the pituitary and from the serum of the pregnant mare

have also been reported to cause descent but the data available are not very convincing At the present time the gonadotropic material from human pregnancy urine is in most instances the best for glandular therapy Since Schapiro s report thirteen years ago a large number of observations have appeared on its use in undescended testes most of which appear to be over enthusiastic A review of all available reports about four years ago by Thompson and Heckel showed that descent was claimed in 61 per cent of the cases on the average including successful results in 55 per cent of 150 intra abdominal testes In contrast to these high percentages of successful results Thompson and Heckel were able to produce descent in only 20 per cent of all their cases and in only 27 per cent of those occurring in patients under sixteen years of age The difference in results may be attributed in part to their exclusion except in the beginning of the study of all testes of the migratory or retracted types

In successful cases descent usually occurs within two months after starting treatment although in occasional instances it may take as long as twenty-one months It is easier to produce descent before than after the age of puberty (27 per cent as compared with 6 per cent in the series of Thompson and Heckel) Descent has been produced however as late as the age of thirty two years

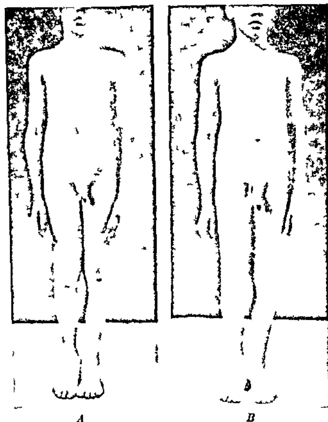


Fig 169—Bilateral undescended testes Growth of genitalia and descent of both testes during treatment with chorionic gonadotropin

A June 11 1938 before treatment, at the age of ten years

B November 19 1938 after 15 000 rat units of A P L showing both testes in the scrotum The left testis became migratory after treatment was discontinued

The position of the testis has an important bearing on the result of treatment According to Thompson and Heckel Descent was produced in nine of twenty one instances (43 per cent) in which the testis was in the inguinal canal in only one of nine instances (11 per cent) in which it was deflected in an abnormal position outside the canal and in none of twenty instances in which it was within the abdominal cavity Descent was produced in one in

stance in which the testis was deflected in the fold of skin to the left of the scrotum

Descent was not produced in any instance in which the testis was deflected over the external oblique muscle or toward the base of the penis Our failure to produce descent in our cases of intra abdominal testes is in striking contrast to the results of some other observers In five of our ten successful cases the testis could either be pulled into the upper end of the scrotum or to a level between the lower end of the canal and the upper end of the scrotum before treatment was started In other words the testes were of the type that commonly descends at puberty In the other five cases there could be little doubt of the influence of the treatment in causing descent

The influence of chorionic gonadotropin on genital growth is more striking than its influence on descent of the testis Marked development of the genitalia may occur without any change in the position of the testis just as during normal puberty illustrating the importance of anatomic factors in preventing descent Examples of genital growth with and without descent are recorded in Figs 169 and 170

W O THOMPSON

RELATION OF GLANDULAR THERAPY TO OPERATIVE PROCEDURES

Treatment with chorionic gonadotropin may be of value before and after surgical procedures Before operation it stimulates genital growth and makes it easier to bring the testis into the scrotum This is important because Thompson and Heckel have demonstrated that operative procedures are necessary in about three fourths of all cases of true cryptorchidism After operation the material may be of value in cases in which the testis is not brought to a sufficiently low level When hernia is present it is not corrected by glandular therapy even if descent of the testis is produced

When glandular therapy is not successful orchidopexy will usually reveal anatomic factors which prevent descent In eleven

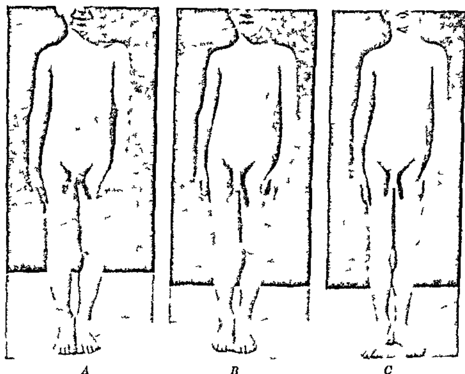


Fig 170—Bilateral undescended testes Marked growth of penis without descent of testes during treatment with chorionic gonadotropin Recession in size after omission of treatment

A November 1 1937 before treatment at the age of five and one-half years

B June 6 1938 after 55 000 rat units of A P L showing marked increase in size of penis but no descent of testes

C July 21 1939 ten and one-half months after omission of treatment, showing decrease in size of penis

patients in the series of Thompson and Heckel these anatomic factors were found to be (1) fibrous bands (all patients) (2) shortness of the structures to which the cord and testis were attached namely the peritoneal process, the transversalis fascia the intercolumnar fascia and the cremasteric muscle and fascia (all patients) (3) abnormal direction of the peritoneal process (four patients), which in three patients was turned upward on the external oblique muscle and in one lay over the rectus sheath and (4) absence of the external ring (one patient)'

W O THOMPSON

STATUS OF GLANDULAR THERAPY

The following facts suggest that chorionic gonadotropin may cause descent only of those testes which would descend normally without treatment at the time of puberty

1 The high percentage of failures with treatment

2 In unsuccessful cases operation has shown anatomic factors which prevent descent

3 The decrease in the incidence of undescended testes after the age of puberty in untreated cases

Influences similar to those introduced artificially come into play during normal development and might be expected to result in descent of those testes not retained by mechanical factors If no more is accomplished with glandular therapy than is accomplished by natural processes at a later age it is pertinent to inquire whether the treatment is worth while The crux of the problem is whether a testis made to descend at an early age with treatment is more likely to be normal than one which descends later without treatment The consensus appears to be that the testis should be brought into the scrotum at an early age although there is some difference of opinion on this question The following points are in favor of glandular therapy

1 It makes it possible to tell at an early age what patients will require surgical intervention by distinguishing between those cases in which descent is prevented by anatomic factors and those in which it is not

2 It causes the testis to move into the scrotum at an early age without operation in one fourth of the cases

3 It facilitates subsequent operative procedures by enlarging the parts involved even when it does not produce descent

If the importance of bringing the testis into the scrotum at the earliest possible age has not been overestimated then perhaps the wisest course to follow in boys with undescended testes is to administer chorionic gonadotropin cautiously and carry out operative procedures if descent fails to occur The age at which treatment should be started is uncertain but if it is to be given at all it should probably be given early perhaps at the age of three years The effective dose and the duration of treatment vary from patient to patient In successful cases descent of the testis usually occurs within two months after the daily administration of from 100 to 1000 rat units is begun After the age of puberty larger doses (as much as 2500 rat units daily) are required The patients must be observed carefully and treatment discontinued before genital growth becomes excessive It has already been pointed out that if treatment is pushed too far a condition simulating premature puberty may result However a moderate amount of genital growth usually must be induced to accomplish the result desired It must be emphasized that little is known about the effect of premature stimulation of the testis with this material on subsequent spermatogenesis and skeletal growth

W O THOMPSON

HYPOGONADISM SECONDARY TO HYPOPITUITARISM

The production of genital growth with chorionic gonadotropin has an important application in the treatment of individuals with hypopituitarism particularly in those of the Frohlich type It may be pointed out that the Frohlich syndrome is characterized by obesity and hypogonadism and often a low basal metabolism There is a marked deposition of fat in the abdomen and thighs with a transverse ridge in the

lower abdomen tending to produce an apron of fat genu valgus and in males the feminine type of breasts The case originally described by Frohlich had a craniopharyngioma of the pituitary but in most instances the sella turcica is normal in size The pituitary appears to be involved and perhaps also the hypothalamic area This condition is described in more detail in the section on the Pituitary but examples of what may be accomplished with chorionic gonadotropin are recorded here in a boy ten years old and in a man thirty seven years old (Figs 171 172) because of their bearing on the conditions already described The susceptibility of this stimulus appears to be less after than before the age of puberty Nevertheless with large doses striking genital growth may be produced in older men It appears that the smaller the genitalia are after the age of puberty the greater the likelihood of influencing their size and the more nearly they approach the normal in size the less the likelihood of doing so If the treatment is given before the age of puberty the fat in the abdomen and thighs may decrease markedly as the genital growth occurs and the skeleton increases in length so that normal body contour is produced Adequate therapy usually produces increased physical and mental vigor In the thirty seven year old man lack of energy and ambition appeared when treatment was discontinued necessitating readministration of the material Without treatment he felt that something was lacking just as a patient with myxedema feels when thyroid is not administered

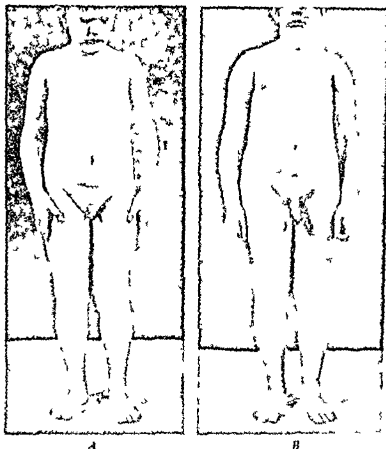


Fig 171 —Effect of chorionic gonadotropin in a boy of the Frohlich type
A September 28 1936 before treatment, at the age of ten years Extremely small genitalia
B February 6 1939 after 5780 rat units of follutein and 569 350 rat units of A P L

W O THOMPSON

TUMORS OF THE TESTIS

Tumors of the testis are rare and occur mostly between the ages of twenty and forty years Their incidence is said to be higher in the cryptorchid testis than in the normal testis although there is some controversy

on this point The tumors may be classified as follows

Malignant.
1 Carcinoma
2 Embryonal teratoma or mixed tumor type including chorionepithelioma

Benign
1 Adult teratoma or dermoid
2 Adenoma of the seminal tubules
3 Interstitial cell tumor
4 Fibroma, lipoma, myxoma

The teratomata may form growths resembling rudimentary fetuses, including the chorion These growths are counterparts of the chorionepitheliomas seen in the female and are just as malignant.

Feminizing Tumors of the Testis.—Chorionepithelioma of the testis is especially interesting to the endocrinologist because in about 10 per cent of the cases there is evi-

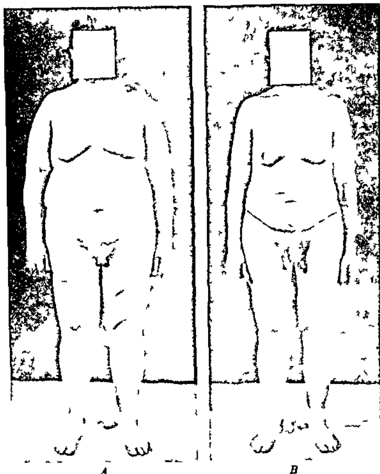


Fig 1 2 —Effect of chorionic gonadotropin in a man aged thirty seven of the Frohlich type, with an undescended right testis

A January 27 1937 before treatment Weight 145 kg Extremely small genitalia No hair on face chest or extremities High pitched voice

B May 16 1938 after 1,325 750 rat units of A P L in two courses Marked increase in size of genitalia Some growth of hair on arms and legs and a moderate amount on the face Voice much lower pitched Greatly increased energy and physical endurance (Contrast with lack of effect upon A P L in Fig 168) After omission of medication decrease in energy and endurance necessitated resumption of treatment (Thompson and Heckel Endocrinology 1940)

The teratoma is the most common form of testicular tumor Next is the carcinoma which has its origin in the adult tubule cells Malignant tumors of the testis are noted for early metastasis by way of the blood or lymph vessels

dence of a feminizing influence This is expressed by enlargement of the breasts sometimes painful and sometimes associated with the secretion of colostrum The Aschheim Zondek test is often positive and in some instances where the pituitary has been

examined, its cells have shown the condition typical of pregnancy In some instances of feminizing tumors, the histology is that of teratoma without the chorionic element

Interstitial Cell Tumors—In any condition involving overgrowth of these cells hypermasculinity would be expected as they are the cells concerned with elaboration of male sex hormone It is *only in children*, however that the full blown picture of the masculinizing effect of these tumors can be noted In adults the effects are not so spectacular as the secondary sex characteristics are already present In the infant or young boy the *genitalia become as large* as those of an adult, accompanied by the rapid skeletal growth muscular development and voice changes that normally occur at puberty Only rare instances have been noted in children although several cases are recorded as developing after puberty

Symptoms of Testicular Tumor—The enlargement is often painless usually develops rapidly and is firm and symmetric There may be quiescent periods There are apt to be enlarged inguinal lymph glands and even the *periaortic lymph glands in the* abdomen are often involved early

Diagnosis—Tumor must be differentiated from tuberculosis which can usually be done by considering the personal and family history and by the fact that in tuberculosis the epididymis and vas are usually hard and nodular Syphilis, with a history of chancre may cause some difficulty in differtial diagnosis because a malignant necrosing growth may give a positive Wassermann reaction although it usually does not affect the result of the Kahn test If in doubt the effect of antisyphilitic treatment should be evident within a short time If there is difficulty in differentiating hydrocele from a tumor, transillumination should be used Hydrocele and tumor may coexist

Treatment.—In the benign types surgical removal is indicated In the malignant types the only hope of cure is an early radical operation with removal of the retroperitoneal lymph nodes along the abdominal aorta This should be done before metastases have formed Irradiation should then be used Provided metastases have not developed teratomata which are resistant to irradiation are the best types for radical surgery Malignant tumors of the testis are usually fatal although life may be prolonged by treatment

W O Thompson

MISCELLANEOUS DISEASES OF THE TESTIS

Orchitis—*Acute Orchitis*—A systemic infection such as typhoid or pneumonia may be followed by acute orchitis (inflammation of the testis), but the chief offender in this respect is mumps Orchitis occurs *in about 12 per cent of patients with this* disease There is marked swelling of one or both testes which are very sensitive to palpation This lasts from three to five days and is associated with a sudden rise in temperature The importance of the condition lies in the fact that in about one third of the cases atrophy of the testis occurs, with subsequent sterility

Chronic orchitis on the other hand is not painful, although the testis slowly becomes swollen and hard The most common cause is tertiary syphilis It may also be caused by tuberculosis, glanders leprosy and certain parasitic diseases

Treatment is directed at the systemic disease of which the orchitis is a manifestation In some instances surgery may have to be resorted to

Hydrocele—This is caused by excessive accumulation of fluid in the tunica vaginalis It may be congenital When acute it is always secondary to inflammation of the epididymis or of the testis as for example in syphilitic infection The chronic type is usually seen in men of middle age Hydrocele caused by such diseases as filariasis may reach an enormous size

Treatment—If the condition is not marked no treatment is indicated Immediate relief in acute cases can be produced by aspiration of the fluid In marked cases surgical procedures are often necessary

Conditions Arising from Interference with Blood Supply—*Extravasation of blood* into the testes is usually caused by injury Sometimes it occurs during breech deliveries The blood supply may be cut off by torsion of the spermatic cord

Infarction of the testis may occur Often

there is no apparent cause It is accompanied by severe pain, *nausea and vomiting* and some fever although the latter is not so high as that noted in mumps The testicular swelling subsides within a week Treatment is palliative

Atrophy —Atrophy may be caused by a variety of conditions *e g* infections, derangement of function of some other gland of internal secretion as for example hypo function of the pituitary, exposure to roentgen rays or radium, permanent interference *with blood supply, pressure such as* that from large varicoceles syphilis etc One of the most important causes is the orchitis which is associated with mumps

Treatment —Depending on the capacity of the testes to respond either substitution or replacement therapy as outlined above is indicated

W O THOMPSON

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DISEASES OF THE FEMALE GONADS

INTRODUCTION

THE ovary serves the function of procreation in women Under stimulus of the anterior *lobe of the pituitary it initiates and* maintains the changes which begin with the onset of puberty and culminate in the full sexual development of the adult woman These changes include the development of the external genitalia of the breasts and secondary sexual characters and the attainment of adult psychosexual status In the adult woman the ripening of the ovum is accompanied by the secretion from the follicular cells of estrogen which causes growth of the endometrium and also prepares the vaginal wall for coitus With the extrusion of the ovum the area of rupture closes and the cells previously follicular take on the character of thecal cells to form the corpus luteum These cells secrete progestin the *function of which is to cause further growth* of the endometrium and increased secretory activity in preparation for the nidation of the *fertilized ovum* In the absence of conception the progestational endometrium breaks down leaving only the basal layer This is accompanied by the flow of nonclotting blood *i e* menstruation

The hormonal control of the ovarian cycle is best understood with reference to artificial menstruation This has been produced by

synthetic hormones both in the castrate monkey and in the castrate woman by the injection of estrogen followed by the injection of progesterone The former produces the type of endometrium associated in the menstruating woman with the ripening of the ovarian follicle, and the latter is the type which is seen premenstrually The former is often referred to as the interval or better the proliferative endometrium The latter is characterized by activity of the secretory glands and is often known as a glandular endometrium A better term is progestational endometrium because of its property of forming decidual tissue for the implantation of the ovum

In monkeys when estrogen and progestin are given together following a preliminary treatment with the former there is a more typical progestational phase than when they are given separately (Engle and Smith 1938) This corresponds to the normal events in the ovary in which the change from follicular to luteal activity is a gradual one Thus in a sense the two hormones act synergistically In another sense they are antagonistic as either tends to inhibit the action of the other This is particularly true of the action of progesterone which produces its characteristic type of endometrium in spite of the simultaneous administration of large doses of estrogen

The changes in the vaginal epithelium can be readily observed by the examination of the vaginal fluid by the method of Papanicolaou (1933) as modified by Shorr (1941) The findings at the time of ovulation consist in a typical appearance of the epithelial cells the disappearance of the polymorphonuclear leukocytes a clean appearance of the smears and the presence of mucus which causes a streaky appearance in the slides (Fig 175) Occasionally red corpuscles are found These may even be visible as overt bleeding and accompanied by pain the well known 'Mittelschmerz' The epithelial cells become navicular in shape, then more square, and discrete in arrangement The nuclei become shrunken and pyknotic and the cells take on the stain for cornification In other words the vaginal mucous membrane takes on the quality of skin These changes are the same as those which occur in other mammals under the designation of 'heat' or estrus Other events in the ovarian cycle can also be followed by the vaginal smears

Menstruation runs parallel as a rule to ovulation That menstruation is not fundamental to ovarian activity is shown by the fact that it occurs only in primates and not in other mammals, whereas estrus and the rest of the ovarian cycle is common to all That menstruation is not directly associated with ovulation can also be demonstrated in the human Anovulatory menstruation is now well known, and the reverse is shown by instances in which conception occurs without menstruation Thus pregnancy has been known to occur in a hypogonadal dwarf Furthermore, a mass of evidence makes it clear that ovulation occurs not simultaneously with menstruation but far from it in the menstrual cycle

This evidence is in general agreement by various methods such as examination of the vaginal fluid, observation of ova in the tubes at operation, pathologic evidence time of a single coitus producing conception, or by estimation of hormones in the blood or urine According to the evidence of the vaginal smears (Papanicolaou 1933) ovulation takes place in most instances on the twelfth or thirteenth day although wide variations occur in individual cases

Since menstruation is the visible event in the ovarian cycle, it is natural that both doctor and patient should focus their attention on it to the exclusion of more fundamental events In fact classification of ovarian diseases is made here and elsewhere on the basis of menstrual disturbances Such a mental habit may lead however to misinterpretations unless the events of the ovarian cycle are kept in mind

The clinical determination of ovarian function includes the history and the physical examination The time of onset of menses length of cycle, duration amount and character of the flow are routine in any history It is important to note the relation of emotional stress obesity malnutrition and other influences to the onset of menstrual disturbances In the physical examination especial attention is paid to secondary sexual characteristics The development of the skeleton figure breasts mammary tissue areolae and the distribution of

body hair is noted The development of the external and internal genitalia is observed Expert gynecologic examination is required to rule out major lesions of the genital tract

HENRY B RICHARDSON

OVARIAN INSUFFICIENCY

This term implies deficiency in the supply or action of estrogen The simplest example is the complete form of insufficiency resulting from castration whether by surgical procedure or radiation This is followed of course by cessation of the menses The endometrium becomes atrophic and cells from the deeper layer appear in the vaginal fluid These are small rounded deeply stained with large nuclei Occasionally no symptoms are noted but ordinarily hot flushes occur These consist of a sensation of warmth starting somewhere in the trunk and spreading over the face causing visible redness and often sweating The latter is sometimes sufficient to require a change of clothing The characteristic which differentiates the flushes from other vasomotor symptoms is the rapid onset and offset usually about five minutes each These are repeated in severe cases many times a day They constitute in themselves a great social disability and in addition to the discomfort are often the inciting cause of repeated upper respiratory infections The next most common symptom is the headache which presents no unusual features A very common complaint is loss of well being often described by the patient as not being her self Nervous disturbances are extremely common as illustrated by inability to cope with situations which formerly presented no special difficulty Any pre existing emotional or psychic difficulty is accentuated such as feeling of inadequacy anxiety state or recurrent mild depressions Occasionally outspoken psychoses are observed including involution melancholia and other disorders

Menopause—The effects of the menopause are extremely variable It may take place with no disturbance whatever particularly in well adjusted persons or it may cause severe symptoms In the severe cases the symptoms are the same as after castration

In contrast to a prevalent assumption the menopause does not necessarily imply a complete cessation of ovarian activity According to the evidence of the vaginal smears a cycle persists in some individuals although this is of slow development and exceedingly long duration A complete follicular reaction may occur, with spontaneous remission of symptoms This may explain the common observation that prior removal of one ovary or part of an ovary accentuates ovarian insufficiency whether due to the climacteric or other cause Removal of the uterus or even partial hysterectomy may be followed by a premature menopause

Amenorrhea—Amenorrhea is the absence of the menstrual cycle at a time of life when menstruation is to be expected One group of cases is that in which the menarche is never established This is referred to as *primary amenorrhea* When this occurs with dwarfism the disease is considered to be pituitary in origin and is best discussed under that section When the skeletal growth is normal there is usually no indication of pituitary disorder beyond minor variations in skeleton and figure For the present these cases are best classified as ovarian in origin since there is no good evidence to the contrary Such individuals continue to have the childish type of figure skeleton genitalia and lack of secondary sexual characteristics They may be obese thus mimicking Frohlich s syndrome or they may be normal in nutrition or thin

Amenorrhea after the establishment of the menarche is known as *secondary amenorrhea* It occurs from a variety of causes of which the chief are emotional disturbances malnutrition obesity and hypothyroidism The striking example of emotional disturbances producing amenorrhea is anorexia nervosa which was formerly confused with Simmonds disease or destruction of the anterior lobe of the pituitary Ordinarily in these cases the amenorrhea is the result of malnutrition but not infrequently precedes it (Richardson 1939 Rahman Richardson and Ripley 1939) The disease occurs in young single women typically within half a dozen years after the onset of the menarche in individuals who show evidence of prior ovarian insufficiency in the form of menstrual disturbances Rarely males are

affected Such individuals lose appetite or more commonly diet to reduce their weight for psychologic reasons The dieting has a compulsive quality as shown by the effect of attempts to increase the weight of the patient against her will This attempt is met by resentment evasions and subterfuges Compulsive behavior in other fields is also evident Most of these patients have gastro intestinal symptoms in the form of ob stinate constipation inordinate use of cathartics and often abdominal pain On recovery of a normal degree of nutrition menstruation is resumed as a rule but in a minority of cases amenorrhea persists

Women who become obese tend to have ovarian insufficiency It is customary to think of the glandular disturbance as pri mary and the result of pituitary disease More often it appears however that the obesity in itself has an adverse effect on the ovarian function Reduction in weight is notoriously difficult particularly when the obesity serves a psychologic function but when accomplished is not infrequently ac companied by a resumption of menses In married women conception following a long period of sterility is occasionally observed after reduction in weight

The cases of amenorrhea associated with pronounced insufficiency of the thyroid gland require no comment here There is a group however in which the evidences of thyroid insufficiency are slight and atypical They have sparse hair a transparent ap pearance of the skin of the face fulness of tissue in the face and legs muscular weak ness and an undue sensitivity to cold, with or without depression of the basal metab olism Such patients often resume menstrua tion with the use of thyroid extract

Ovarian Insufficiency with Persistence of the Menstrual Cycle —This group com prises the great bulk of patients with ova rian insufficiency They are the ones in whom there is a disturbance of the menstrual function alterations in the rhythm or dura tion or quantity of the menstrual flow It is precisely in this group that it is most dif- ficult to arrive at a diagnosis When the menses become infrequent scant or of short duration this may be taken as evidence of ovarian insufficiency and the diagnosis can be confirmed by vaginal smears taken at the time of expected ovulation Confusion arises when the menstrual flow is excessive, as will be described below

Treatment of Ovarian Insufficiency — Ovarian insufficiency, in the sense of a lack of estrogen is treated by supplying the missing hormone Stimulation of the ovary by means of extracts of the anterior lobe is theoretically sound but the dosage is greatly limited by the local reaction which such extracts often produce The extract of preg nancy urine is gonadotropic in animals but in man appears to be predominantly a male principle which finds its most striking ap- plication in the treatment of undescended testicle or in gonadotropic stimulation of the male Androgens produce complete ovarian insufficiency Progesterone has but one function and that is to form a progesta tional endometrium Thyroid is useful in appropriate cases For the most part how ever, the choice of preparations is limited to estrogens

The basic principle of treatment in ova rian insufficiency is the same as in other diseases to give enough of the preparation to produce the intended effect as demon strated by objective criteria The latter are conveniently furnished by the examina tion of the vaginal smears (Figs 173-176) The *aim of treatment* is best attained by the use of injections and is concerned with the nature of the preparation dosage method of administration and schedule whether continuous or intermittent Either of the estrogens may be used estrone or estradiol The dosage is expressed in rat units rather than milligrams That amount of the agent is given which produces the vaginal smear which is found in normal women at the time of ovulation *i.e* the follicular type This amount varies from case to case even in complete ovarian insufficiency The ordinary range is 2000 rat units three to five times a week occasionally higher The material comes dissolved in sesame oil and is injected by means of a size 22 needle 1½ inches in length Injections are best made into the upper part of the buttock although other sites may be used particularly if the pa tien is to give the injections herself When enough hormone is given to produce the typical follicular smear the remission of symptoms may be noted and subsequent

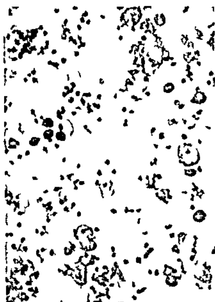

Fig 173


Fig 174


Fig 175


Fig 176

Figs 173-176.—Primary amenorrhea The use of the vaginal smear as a guide to estrogenic therapy (Courtesy of Drs Papanicolaou and Shorr) This series to illustrate also the castrate and postmenopausal cases in which the same initial smear and the same reaction to therapy are observed

Fig 173—Atrophic smear in primary amenorrhea

Fig 174.—Change in smear following estrogenic therapy

Fig 175.—Follicular smear maximum effect induced by estrogenic therapy This is referred to as a follicular reaction because it is the normal accompaniment of the full development of the ovarian follicle in a menstruating woman

Fig 176—Pseudomenstrual or withdrawal bleeding This occurs regularly when treatment is stopped at an interval which is usually five days after cessation of estrogenic therapy

treatment given by the oral route on a more empiric basis

Besides establishing the dose it is necessary to decide whether or not the treatment should be continuous To imitate as far as possible the normal events in the ovarian cycle it is necessary to give the injections intermittently Further compelling reasons

for this are several Continuous treatment results in hyperplasia of the genital organs and may cause bleeding even while the treatment is being *continued* When the medication is discontinued after long periods the bleeding which results from the with drawal may be profuse and even alarming Further the possibility of inducing cancer by large doses though remote cannot be *disregarded* It is best therefore to give a course of injections over three weeks or at the most four weeks to discontinue them for ten days or so and then to resume

The *danger of the induction of cancer* need not be overemphasized It has been produced in animals by estrogenic therapy only by huge doses consisting of many units relative to the animal used By the above method the effect is to give one human unit and no more Cancer occurs spontaneously in women in the fourth decade or later that is after twenty years or more of periodic secretion of one human unit of estrin It is a question therefore whether cancer is related in women to estrogenic activity or the lack of it Reports of cancer in the course of estrogenic treatment are so rare as to suggest that it occurs as a coincidence

The advent of efficient preparations for *oral use* does not alter the fundamental principles of estrogenic treatment These preparations can be used to replace injections even when it is desirable to produce a maximum effect as demonstrated in the vaginal smears Their practical use however is affected by the fact that often a follicular reaction for reasons to be stated below cannot be reached promptly if at all Oral therapy may be inadequate for cases which need rapid relief for instance when the ovarian insufficiency is associated with mental symptoms When the menopausal syndrome is atypical or occurs with nervous manifestations such as anxiety or depression the relation of the symptoms to ovarian insufficiency is often obscure and can be established only by a therapeutic test This consists as stated in giving enough treatment to produce a follicular reaction in the vaginal smear In such cases the most efficient treatment is often to give injections from the start In other instances a less rigid procedure is sufficient Many women are completely relieved of symptoms with only a partial follicular response In such cases no object is gained by increasing the dose

It is fortunate that this is so because the physiologic effects which can be produced by oral treatment are often limited With the natural estrogens or their derivatives the limiting factor is the absorption through the intestinal wall which is only 5 to 10 per cent of the oral dose on the average To allow for the partial absorption the price has been adjusted and the dosage increased The effects of injections can thus be obtained but not in all cases

The newer preparations of stilbestrol or its compounds have been widely studied (See Shorr *et al* 1939 Taylor and Thompson 1941) These are cheap and are readily absorbed when given by mouth moreover they produce all the effects of the natural estrogens On the other hand they often cause unpleasant symptoms among which nausea and vomiting are by far the most common Drowsiness skin rashes vertigo and thrombocytopenia have also been observed Permanent damage as the result of stilbestrol therapy has not been demonstrated One case at least of hepatitis has been observed but this was thought to be a coincidence The incidence of the untoward effects varies in different reports from a small minority to the figure of 80 per cent given by Shorr *et al* (1939) My own experience is between these extremes Occasional patients react unfavorably even to small doses but in general the greater the dose the greater the likelihood of unpleasant effects In practice the usual dose is 1 to 2 mg every twenty four hours

The principle of giving the treatment intermittently is just as important in oral therapy as it is with injections and is much more difficult to enforce because of the convenience of the oral route Just enough stilbestrol should be prescribed to cover the intended period of treatment Apart from other considerations mentioned above any effective estrogen in big enough doses is likely to produce uterine bleeding during prolonged administration or serious hemorrhage when the treatment is stopped The efficiency of stilbestrol makes this a very practical problem For instance Taylor and Thompson (1941) in their series of thirty

cases report four patients who had severe uterine bleeding in the course of the treatment or immediately afterward The doses with one possible exception were distinctly moderate but were continued over a period of eight to nine months

Application of Treatment to Special Disorders —The treatment of *castration* and the *menopause* has been indicated in the preceding paragraph The results which may be expected are first the relief of hot flushes In nearly all cases this is solely a question of adequate dosage The same often applies to headaches which are associated with the menopause It is probable also that there will be a more or less complete restoration of the sense of well being Other symptoms which occur with the menopause may or may not be relieved No object is gained by pushing the dose beyond the quantity necessary to produce a follicular type of smear but if symptoms persist the treatment should be continued with the intermissions mentioned over a period of two or three months before passing judgment as to its efficacy The estimate of the effect on psychic disturbances is complicated of course by the influence of suggestion Pronounced effects are observed in some cases and none whatever in others apparently exactly similar

In the cases of patients with *primary ovarian insufficiency* who fail to undergo puberty and never menstruate the question arises whether to treat them or not The problem is individual and social Often there is a strong sense of inadequacy the patient naturally feels very incomplete as a woman This is one indication for treatment Much depends also on the social economic status If the patient can support herself in a sheltered position without much professional contact with other people there is less reason for treatment If on the other hand she is dependent on her parents as is usually the case the physician must look forward to the time when the parents will no longer be living The status of a patient with inadequate physical and emotional equipment alone in an adult world is not enviable It is usually wise therefore to recommend a prolonged trial with replacement therapy emphasizing the fact that it is replacement therapy and nothing more After full doses have been given over a prolonged period of perhaps a year and a half the patient will be in a position to judge whether to continue It should be pointed out that menstruation is not to be expected as the result of the treatment and that regression will take place on cessation There is a possibility however that the ovaries will assume their own cyclic activity

The treatment of *amenorrhea occurring after puberty* varies with the cause The patients with anorexia nervosa respond little to glandular treatment of any kind Psychotherapy is effective in the milder cases particularly those in which a situational factor is predominant These individuals benefit by the opportunity to talk out their personal problems The more severe cases are the result of a prolonged and deep seated neurosis are resistant to psychotherapy and improve if at all only after a prolonged course of psychiatric treatment

Women who stop menstruating when they become obese are best treated with reduction of weight as indicated in a preceding paragraph Amenorrhea in unsuspected thyroid insufficiency has also been referred to

Patients with *mild ovarian insufficiency* as indicated by scant irregular or infrequent menstruation may be treated by replacement therapy when the symptoms warrant it The demonstration of the insufficiency by the technic of the vaginal smears requires examinations over a long period and it is in these cases that the estimation of the smears is difficult The treatment is complicated by the fact that when the menstrual cycle is present the use of the hormone even in physiologic doses may disturb it Treatment is best reserved for the intermenstrual period beginning after the cessation of flow and ending about five days before the expected onset of the next bleeding In these cases of mild insufficiency attention to psychogenic and dietary factors is particularly fruitful

The hormonal treatment of *dysmenorrhea* is tentative Estrogens and progestin have been used There is no uniform agreement as to the results

Masculinization —Masculinization might be regarded as a form of ovarian insufficiency relative to an excessive supply of androgens Such a concept serves to call attention to the fact that just as the male

secretes estrogen, the female secretes androgen Sexual characteristics depend on the predominance of the respective hormone Masculinization occurs as the result of excessive production of androgens by the female usually in the adrenal cortex as the result of hyperplasia or tumor Corroborative evidence of a lesion in this location is a substantial rise in the urinary excretion of 17 ketosteroids (Fraser *et al* 1941) Masculinizing tumors occur less commonly in aberrant adrenal tissue in the ovaries or attached to them and have also been reported elsewhere in the midbrain pituitary pineal gland and in the thymus In young girls the disease is known as *pseudosexual precocity* (Reilly *et al* 1939) because of the growth of pubic hair and enlargement of the clitoris but the development of adult female characteristics which is the function of estrogen is usually lacking In the adult woman frank masculinization takes place with changes in the voice hirsutism and enlargement of the clitoris The *treatment* is removal of the tumor

Minor grades of excessive androgenic activity are frequently observed or rather suspected in the clinic Possibly a manifestation of this is the hypertrichosis which is so frequently observed androgens are known to produce this It is also possible that excessive hair is an atavistic survival It occurs in a great number of individuals without any necessary relation to their status as women There is also an ill defined group in which the skeleton musculature body hair and voice approach the male type These cases are not sufficiently understood for discussion at the present time

Henry B Richardson

DISEASES OF HYPERSECRETION

Prolonged or excessive action of estrogen is thought to be one of the causes of functional uterine bleeding Otherwise evidence of such excess is rare It is detectable mainly before puberty or after the menopause In young girls it is caused by *neoplasms* of the ovary the granuloma cell tumors The result is a true sexual precocity with all the evidences of estrogenic effects plus menstruation (Reilly *et al* 1939) Genital and sexual development approaches the adult type Rare cases of sexual precocity with disseminated osteitis fibrosa and skin lesions both of peculiar distribution have been described (Albright *et al* 1938) In older women mostly after the menopause thecal cell tumors of the ovary have been described The hormonal effects of these tumors are not clear cut The treatment is removal

Henry B Richardson

FUNCTIONAL UTERINE BLEEDING

Functional uterine bleeding may be defined as that which occurs in excessive amounts or at unexpected times in the absence of gross lesions It is due to dysfunction of one or more of the hormones ovarian or pituitary which are concerned in the ovarian cycle

Bleeding occurs experimentally and clinically as the result of any procedure by which the supply of estrogen to the body is diminished (Engle *et al* 1935) Thus it is observed after ovariectomy and is a regular occurrence on the interruption of therapy with estrogens (see Fig 176) Complete withdrawal is not necessary since diminution of the supply to a lower level suffices to produce bleeding On the other hand prolonged administration of estrin to castrated monkeys results in bleeding even while the administration is being continued The bleeding which occurs experimentally from a decrease in the supply of estrogen can be inhibited by the administration of progestin and this effect is not prevented by the simultaneous administration of estrogens (Engle *et al* 1935) When the administration of progestin is discontinued bleeding takes place in the form of menstruation

It is not clear to what extent this mechanism applies to spontaneous bleeding in the human In fact the opposite theory namely excessive action of estrogen is the one which is most frequently upheld Attempts have been made to establish the etiology on the basis of the endometrium as studied histologically The greatest emphasis has been put on the hyperplastic endometrium an exaggeration of the type which normally is observed with the development of the ovarian follicle Such bleeding is associated with

follicular cysts of the ovary and usually but far from invariably with the absence of corpora lutea The theory is that because of the failure of ovulation the follicles of the ovary secrete estrogen continuously instead of intermittently and that as the result the endometrium becomes fixed in the hyperplastic stage Bleeding therefore takes place without the formation of a progestational endometrium and without the rapid desquamation of the latter which is characteristic of normal menstruation Bleeding may occur, however with any type of endometrium atrophic proliferative hyperplastic or progestational In addition irregular shedding and irregular ripening has been described The incidence of the hyperplastic type according to Jeffcoate (1937) has been overestimated and does not exceed one third of all the cases

Classification of bleeding by hormonal assay has been attempted but the results are uncertain More knowledge is needed concerning the chemical changes which occur in the metabolism of the sex sterols Vaginal smears may be done but require long experience for interpretation in these patients

Bleeding may occur with cyclic ovary activity whether the cycle is prolonged short or normal When it occurs twice a month the alternate bleedings are probably associated with the follicular stage of the ovary and are of no great clinical significance the Mittelschmerz of the German writers This phenomenon does however demonstrate the fact that bleeding can occur as the result of the action of estrogens Bleeding in excess at or following menstruation is known as *menorrhagia* and bleeding which is noncyclic as *metrorrhagia*

Attempts to classify bleeding with respect to age or the menstrual history in terms of the etiology have not been widely accepted Bleeding from a hyperplastic endometrium occurs however most frequently with puberty and often with the menopause (Jeffcoate 1937) and that which is associated with a progestational endometrium nearly a decade earlier than the latter It may take place however at any time during the child bearing age

Functional uterine bleeding is very common At best it is a social and marital disability, and at worst produces chronic anemia and not infrequently threatens life The indications for treatment are to stop the bleeding and if possible to prevent operations on the pelvic organs or radiation and the distressing effects which so often follow in their wake Since the clinical and pathologic classifications leave much to be desired the treatment is empiric

Treatment —The hormones may be discussed in the order of the frequency with which they have been used The indications have been stated at length by Jeffcoate (1937) and Hamblem (1939) The use of *anterior pituitary like extract* of pregnancy urine has been reported most extensively with good results by most authors and no benefit by a few Some of the cases in each series, usually a minority fail to receive benefit This was first employed with the idea that it would stimulate the corpus luteum and thus convert a bleeding hyperplastic endometrium into the progestational type which precedes normal menstruation The human being is not however one of the species in which this extract has a pronounced luteinizing effect on the contrary this action is said to be slight The androgenic effect of this extract on the male suggests an action similar to testosterone of this however there is no evidence Such extracts may produce local irritation and even a constitutional reaction with fever These effects seem to have been more common with the earlier preparations than at present If time permits it is advisable to give a preliminary dose of 0 2 cc This may be followed on the second day with 250 rat units to be repeated on the next day and three times a week Kurzrok (1937) recommends 200 to 500 rat units daily during active bleeding Any standardized preparation from a reliable company may be used Bleeding often ceases within a few days

Androgens have been used more recently but with a greater unanimity as to their action and a higher proportion of successes (See Geist *et al* 1938) *Testosterone* inhibits experimental bleeding and suppresses menstruation in the monkey also in the normal menstruating woman (Papanicolaou Ripley and Shorr 1939) It decreases the size of the ovaries and inhibits follicular activity Thus it produces a temporary men

opause It may cause hirsutism lowering of the pitch of the voice and enlargement of the clitoris but so far no lasting ill effects have been detected experimentally or clinically except for the persistence of slight excess of hair There are numerous androgens which vary in their chemical constitution and in their effects some of them approaching the estrogens The dosage in terms of testosterone propionate is 25 to 50 mg three times a week Bleeding should stop in a few days

The effect of *estrogen* has been little studied as it is contrary to theoretic indications in cases with hyperplastic endometrium (Jeffcoate 1937) It is said to be indicated only in the presence of an atrophic endometrium Scattered reports of its use are available with dramatic cessation of bleeding in some cases The dosage may be chosen as that which is effective in the menopausal syndrome namely from 2000 rat units intramuscularly three times a week to 3000 rat units daily Either estradiol or the estrone form may be used

The use of *progestin* has been suggested for several years but it has become available on a large scale only recently It is still very expensive It inhibits experimental uterine bleeding in monkeys and has been urged on theoretic grounds in cases of hyperplastic endometrium The treatment is expected to inhibit the bleeding and on cessation to be followed by a normal menstruation The dosage is much less than the amount necessary to produce a progestational endometrium in a castrate woman One Corner-Allen rabbit unit = 1 mg Doses of 5 to 10 mg daily have been used

From the preceding discussion it is evident that the hormonal treatment of bleeding is in the empirical stage with respect both to the selection of cases and the choice of preparation and dosage Unlike the estrogenic treatment of the menopausal syndrome there is no convenient method for determining the size of the dose necessary to produce the optimum effect

The choice lies at present between testosterone and anterior pituitary like extract of pregnancy urine with perhaps a slight advantage in the former If one preparation fails another may be tried Progesterone is theoretically sound in cases except those which already have a progestational type of endometrium Recommendation for general use would be premature Estrogens have a dramatic effect in a small group of cases which cannot be selected in advance If effective the bleeding stops in three or four days The *evaluation on empirical grounds* of any form of therapy is difficult This has been emphasized by Geist (1935) who attributes all the reported beneficial effects of extract of pregnancy urine to coincidence. This again calls attention to the intermittent nature of the bleeding and the necessity for conservative treatment

By definition the type of bleeding under discussion is that in which no gross lesions can be demonstrated The presence of certain lesions is not however a contraindication to hormonal therapy The relation between fibromyomata and endometrial bleeding has been discussed by Blair (1936)

Treatment without Hormones —This may be mentioned though well known Rest in bed ice bags and attempts to increase the coagulability of the blood are used For the latter purpose a high calcium diet mainly milk calcium lactate 5 grains (0.3 Gm) 2 tablets three times a day and viosterol 5 to 10 drops daily may be used. Snake venom is mentioned in the literature Curettage may be necessary to stop alarming hemorrhage Bleeding is spontaneously intermittent and repeated curettage is preferable for the reasons mentioned to more radical procedures

Bleeding occurs in association with ovarian dysfunction of some sort under the same conditions as menstrual irregularity or secondary amenorrhea Attention to the same etiologic factors may be very fruitful in functional bleeding These include psychogenic factors caloric undernutrition avitaminosis and thyroid insufficiency Such treatment has the advantage of being directed at the cause rather than the symptom

HENRY B RICHARDSON

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PUBERTY

Puberty is the change from childhood to maturity The physiologic and psychosexual adjustments required during this process are difficult at best The emotional disturbances occurring at this time are varied and often reawaken maladjustments which existed in early childhood The problem is frequently complicated by the attitude of the parents in particular the mother, who tends to reinforce the natural reluctance of the growing child to assume adult status

To puberty in general is added the psychologic effect of the menarche itself that is of genital bleeding To many girls this is alarming particularly if unexpected For instance a child may be too ashamed to tell anyone about it

Puberty is a very gradual process which becomes complete only after the lapse of several years (Fluhmann 1939) It is initiated by the pituitary The first change is the increase in the size of the follicles of the ovary together with the appearance of secondary sexual characteristics as in the breast and appearance of estrogens in the urine This initiation of estrogenic activity occurs in the eighth to tenth year *i e* three to five years before the average menarche Further evidence of estrogenic activity is the menarche Ovulation may or may not occur anovulatory menstruation is common in the first few cycles Further development of genitalia and secondary characteristics is very gradual Complete fertility is not attained until the sixteenth to the nineteenth year Thus the physiologic changes may require ten years Psychosexual maturity comes last and may not be complete until the early twenties even in well adjusted individuals

Anxiety of parents is usually aroused by absence of menstruation at the expected time failure to grow according to preconceived standards or by obesity They usually attribute the last to endocrine disturbances The probable age of onset of menstruation may be judged first from statistics and second from the age of menarche of the relatives Statistically a peak is observed at thirteen years (Engle and Shelesnyak 1934 Fluhmann 1939) The curve falls off rapidly in either direction Five to 10 per cent of normal individuals begin to menstruate between eleven and twelve years of age but menarche before ten or eleven years is outside the normal range At the other end of the scale also more than 5 per cent of normal girls begin to menstruate at fifteen to

sixteen years of age Delay to sixteen, seventeen, or even twenty years is compatible with childbearing

Anxiety concerning height is warranted if growth stops Ordinarily this is not the case but rather the height is less than the parents think it should be In estimating the future height of the child a rough guess may be made from the height of the relatives Further growth may be predicted if the epiphyses remain open Increase in height beyond the limits fixed by heredity is improbable

Delayed menarche is of more concern when accompanied by other evidences of retarded development and of less moment when associated with normal growth and sexual characteristics When both menstruation and sexual development are delayed beyond the probable range of normal a pronounced ovarian insufficiency may be inferred When the growth factor is also lacking a probable diagnosis of pituitary insufficiency may be made

At puberty ovarian function may be depressed by the same influences which operate during adult life namely emotional disturbances overnutrition or undernutrition avitaminosis and thyroid insufficiency A common syndrome is obesity, moderately low basal metabolism and amenorrhea This is usually unrelated to thyroid insufficiency Shelton (1933) has called attention to a group of children in whom retardation of epiphyseal growth is the only indication of thyroid insufficiency In the absence of retarded bone development the diagnosis of thyroid insufficiency is not warranted unless the basal metabolism is minus 20% or below or clinical signs of thyroid disease are present

Functional uterine bleeding is common shortly after the establishment of the menarche and has been discussed in an earlier section

Treatment—Most problems at puberty are concerned primarily with anxiety of the parents In the great majority of cases puberty progresses to maturity regardless of interference on the part of the physician The indications are, therefore in favor of extreme conservatism General measures are to be preferred to endocrine therapy directed at the stimulation of ovarian function They are also more effective The most important of these, as well as the most difficult, is *psychotherapy* This should be begun by the mother long before the menarche by explanation designed to prepare the daughter for this event Many women have bizarre notions about menstruation reminiscent of the beliefs of savage peoples They have the idea that menstruation is a means of getting rid of bad blood Thus, delayed menarche to them is not only a defect but also a positive threat to health Explanation of the physiology of menstruation is therefore in order Fortunately, in many cases reassurances at frequent intervals is all the psychotherapy that is needed

Correction of nutritional disorders is frequently called for *Reduction of weight* is best accomplished by dietary means This may encounter resistance from the mother who excuses herself on the ground that dieting may be injurious to the child It may be necessary to support the child against the mother Explanation should be given that the only danger is avitaminosis and directions should be given for combating the latter Malnutrition due to external causes and avitaminosis should be corrected malnutrition from psychic causes is extremely difficult to overcome Thyroid extract may be given for thyroid insufficiency The daily dose may be started at 1 grain (0 06 Gm) and increased ½ grain each week until minor toxic symptoms occur It should then be reduced to about two thirds of the toxic dose and continued for months except for intermissions of one week per month When the physician is under pressure to give some form of glandular treatment thyroid extract is to be preferred to injections of estrogens or gonadotropic preparations

If *puberty* is *delayed* to a *pathologic extent* it may be necessary to try gonadotropic or estrogenic preparations First it is necessary to know whether or not pubertal changes are taking place For this purpose permanent records are indispensable This applies obviously to height and weight which may be compared with previous observations at school Photographs of the figure and genitalia are extremely valuable for reference and accurate descriptions of sexual hair and development of breasts are very helpful Rectopelvic examinations are useful

in skilful hands Objective evidence of growth may save the child from the necessity of injections Apart from possible injurious effects on the developing pelvic organs these are undesirable because they suggest to the child inadequacy or illness They are best postponed to the age of fifteen or sixteen depending on the age of the menarche in the relatives The specifications for treatment are the same as in the adult

Functional uterine bleeding occurring shortly after puberty is commonly reported in gynecologic practice It is said to be more readily controlled by glandular treatment than any other group of cases Spontaneous improvement may be suspected The necessity for conservatism in respect to surgical measures or radiation is obvious

HENRY B RICHARDSON

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DISEASES OF THE LOCOMOTOR SYSTEM

DISEASES OF THE MUSCLES

CLASSIFICATION OF DISEASES OF THE MUSCLES

I Parenchymatous myositis
- (A) Suppurative myositis
  - 1 Primary suppurative myositis
  - 2 Secondary suppurative myositis
- (B) Nonsuppurative myositis
  - 1 Dermatomyositis
  - 2 Primary myositis fibrosa
  - 3 *Trichinous myositis*

II Myopathies

III Interstitial myositis
- (A) Myositis ossificans
  - 1 *Progressiva*
  - 2 Traumatica
  - 3 Circumscripta
- (B) Intramuscular fibrositis
  - 1 Primary intramuscular fibrositis (muscular rheumatism lumbago torticollis)
  - 2 Secondary intramuscular fibrositis

Myositis signifies an inflammation of muscle myopathy means any disease of muscles The term myositis is generally used however to indicate inflammatory presumably infectious diseases of muscles The term myopathy is usually reserved to designate a group of disorders which is associated with slow progressive loss of power and atrophy or hypertrophy of the muscles the main lesion is in the muscles and not in the somatic motor system but the relation with the autonomic nervous system is not well understood Myalgia merely indicates pain in the muscles It is a symptom of many diseases such as influenza Malta fever and dengue and of poisoning with lead and arsenic When used as a diagnosis it is a confession that nothing is known regarding the disease except that the patient complains of painful muscles

Considering the fact that everyone is affected with some disease of the muscles at least once but usually many times in his life and in view of the relative availability of the muscles for biopsy it is strange that so little is known about diseases of the muscles even about the most common type muscular rheumatism

A distinction should be made between diseases which primarily affect muscle cells and the supporting fibrous tissues simultaneously and those which primarily affect the supporting fibrous structure of the muscle and in which the muscle cells remain unaffected or are *only* secondarily involved Thus a distinction should be made between parenchymatous myositis the myopathies *and the much* more *common interstitial* myositis

Charles H Slocumb

PARENCHYMATOUS MYOSITIS

Parenchymatous myositis is a disease of the muscles which simultaneously affects the muscle cells and the intramuscular fibrous supporting tissue It may be suppurative or nonsuppurative It may appear without localized infection elsewhere but in most cases it is part of a systemic infection or pyemia or it results from extension from an infected viscus bone joint or wound

SUPPURATIVE MYOSITIS

Primary Suppurative Myositis—Primary suppurative myositis may affect one or more muscular regions It is of bacterial origin and its course may be acute or chronic It has been called a primary disease because the mode of entry of the infection has not been found Certain special forms are observed in the tropics (Miyake Sayers and others)

Etiology—Trauma bruising strain and exposure to cold or dampness have been regarded as predisposing causes of primary suppurative myositis *Staphylococcus aureus* is the organism most frequently found in the abscesses in the muscles however other organisms have been found Either sex and any age group may be affected although in most cases the patients are young men

Morbid Anatomy—There may be one or multiple abscesses or there may be a diffuse infiltration in the muscles When the abscess is close to the surface the skin and

subcutaneous tissue may also be inflamed The affected muscle is edematous friable and appears red or gray Microscopic examination of the walls of the abscess during the acute stage reveals bacteria and evidences of acute serous serofibrinous or purulent inflammation The abscess contains pus fragments of necrotic tissue and blood During the chronic stage granulation tissue is present Healing takes place by scar formation

Symptoms—The onset of symptoms is usually sudden Headache fever chills and sweating are soon followed by localization of pain and swelling in the affected muscles Fluctuation occurs in four to ten days and the abscess rarely resolves without evacuation of pus A single abscess well drained may heal in a few weeks When multiple abscesses occur the patient may be confined to bed for months

Diagnosis—The localized painful fluctuant swelling in a muscle usually makes an early diagnosis relatively easy but if the affected region is juxta articular a diagnosis of pyoarthrosis is sometimes entertained

Prognosis—The prognosis is good if the abscesses are drained early Miyake reported one death in thirty three cases and Sayers reported two deaths in twenty six cases After the abscess heals the muscle usually recovers good function In severe cases there is much destruction of muscle with replacement by scar tissue which may lead to deformity when it contracts

Treatment—Hot applications may be applied during the early stage of the infection to hasten localization As soon as fluctuation is present the abscess should be freely drained by a broad incision It is better to err by opening an indurated region than to allow an unrecognized collection of pus from suppurative myositis to infiltrate the surrounding tissue Earle (1939) treated eighteen patients with sulfapyridine giving 2 Gm a day for five days and repeating the course if necessary All of the patients improved rapidly and recovered Surgical procedures may not be necessary if the patient responds well to sulfapyridine If contractures ensue massage and orthopedic corrections should be used

Secondary Suppurative Myositis—Secondary suppurative myositis is associated with other dominant infection elsewhere in the body The infection may reach the muscle because of a pyemia or by extension from an adjacent infected viscus bone joint or wound The most common causative organisms are the staphylococcus, streptococcus tubercle bacillus and *Treponema pallidum* The disease may be associated with actinomycosis gas gangrene and erysipelas

CHARLES H SLOCUMB

NONSUPPURATIVE MYOSITIS

Dermatomyositis—Dermatomyositis is a nonsuppurative inflammation of the skin subcutaneous tissue and skeletal muscles which begins with vague and indefinite prodromata It may have an acute subacute or chronic course but generally is chronic

Etiology—The etiology is unknown but most investigators believe that some infection is the cause Chilling exposure and fatigue may also be of etiologic importance The disease usually affects persons who are between the ages of twenty and forty years although it may occur in any decade of life Sex and season have no apparent influence

Morbid Anatomy—Characteristic pathologic changes are found in the skin and in the skeletal muscles At first the skin becomes thickened firm and edematous The affected muscles become pale yellow or red appear swollen and permeated with yellowish serum, and may feel soft or firm Microscopic examination reveals perivascular lymphocytic inflammatory reaction in the affected muscles and subcutaneous tissue, and parenchymatous degeneration of muscles The increase in connective tissue and thickening walls of the blood vessels are slight

Symptoms—Early acute symptoms may be fever prostration dermatitis with or without edema and muscular weakness and pain More often the onset is subacute or insidious with general malaise weakness low fever dermatitis and muscular aching from myositis The signs of dermatitis or myositis may assume the dominant role and the other be overlooked however within a few months both are usually apparent

The dermatitis may be a prominent finding or may be transitory it may appear as

a dusky erythema with or without edema or it may simulate pellagra toxic erythema urticaria poikiloderma light sensitivity, or other conditions Edema especially around the eyes and face and over the affected muscles, may be transitorily present The dermatitis may be persistently present or may disappear leaving the skin normal or pigmented The eyelids often are a dusky erythematous color and may be edematous The fingers occasionally have a similar color but rarely present a Raynaud like syndrome

The affected muscles are usually weak moderately tender and firm or boggy to palpation and moderately painful with use During an acute stage the affected muscles may be too weak and painful to use painful even during rest and very tender to pressure Muscle atrophy and fibrous contractures may limit the range of movement of joints but demonstrable intra articular disease does not occur The temperature may be as high as 102° to 104° F or as low as 99° to 101° F The patient may not be aware of the fever Subjective symptoms of stiffness and aching made worse by inactivity may be present but are minimal considering the amount of disability present The course may be rapid terminating fatally in a few weeks but more often relapses and remissions occur over a period of months or years Microscopic study of a biopsy specimen of the affected muscle and skin is usually necessary to substantiate the suspicion of the clinical diagnosis Less significant findings which are occasionally present are dysphagia transitory eosinophilia decreased electric reaction of muscles decreased tendon reflexes splenomegaly lymphadenopathy sensory changes and abnormalities of creatine creatinine excretion

Polymyositis hemorrhagica is probably a form of dermatomyositis but it differs from the usual form of this disease in that there are hemorrhages in the muscles and into the skin The onset is more sudden and the course more acute and this form of the disease is more frequently associated with nephritis and cardiac involvement than is the more common type of dermatomyositis

Diagnosis—When symptoms and signs are well established they are usually sufficiently characteristic of dermatomyositis but in the early stages of the disease a biopsy of skin and muscle is usually necessary to establish the diagnosis Not infrequently it is difficult to distinguish dermatomyositis from scleroderma, scleredema or lupus erythematosus In scleroderma the course is usually more uniformly chronic and there is little or no fever, a Raynaud like syndrome sclerodactylia possibly trophic ulcers the microscopic findings of thickened blood vessel walls and more increase in fibrous tissue and less inflammatory infiltration than in dermatomyositis (Brock) In scleredema the edema and skin changes clear completely In lupus erythematosus the dermatitis is more limited to exposed parts of the body and there are leukopenia kidney irritation arthralgia stomatitis and characteristic biopsy findings

Prognosis—The prognosis is unfavorable Steiner collected from the literature seventeen out of twenty eight cases and Brock forty out of seventy five cases in which the disease proved fatal There often are remissions and exacerbations of symptoms Spontaneous arrest of the disease for more than ten years has been observed (O Leary) Death may result from bronchopneumonia, or from respiratory or cardiac failure resulting from involvement of respiratory muscles muscles of deglutition or the cardiac muscle

Treatment—Treatment is for the most part symptomatic It consists of rest in bed local application of heat light massage and special therapeutic exercises to minimize contractures For relief of pain salicylates acetylsalicylic acid or aminopyrine are usually adequate, when symptoms are severe morphine may be required Brock recommended removal of obviously infected foci and injection of typhoid vaccine Glycine, prostigmin pilocarpine and ephedrine have been tried without apparent help (Turner Marcus and Weinstein)

Progressive Myositis Fibrosa—Progressive myositis fibrosa is a localized or generalized subacute or chronic inflammation of a muscle and its fibrous tissue The muscles that are involved atrophy and are eventually almost completely replaced by fibrous tissue There have been only thirteen cases of generalized myositis fibrosa reported in the literature

Etiology—The etiology is unknown The

incidence of the disease bears no apparent relation to sex

Morbid Anatomy.—Muscle most recently affected may appear swollen Later, the muscles atrophy, feel firm and when cut grate on the knife The muscles chiefly involved appear white, those which are less severely affected are reddish yellow On microscopic examination some muscle fibers are seen to be larger than normal others are atrophied Hyaline and hydropic degenerations occur and there is a loss of transverse striations There are local increases in fibroblasts and lymphocytes with a few plasma cells and neutrophilic polymorphonuclear leukocytes Fibrous tissue eventually replaces the diseased muscles Schwab Brindley Bodansky and Harris report a marked creatinuria, decreased ability to store creatine in the muscles and a low creatine content in the affected muscles Ornsteen however did not find creatinuria in the case which he reported

Symptoms.—The onset is insidious A voluntary muscle or a group of such muscles usually in the lower extremities is first involved Clinical features are weakness sweating rapid pulse and respiration loss of weight stiffness of the muscles and clumsiness At first there is a doughy feel to muscles but later a boardlike hardness is observed Severe muscle spasms may occur

Finally the muscles atrophy and are replaced by fibrous tissue Severe contractures may occur Pain and tenderness are not prominent in the early stage of the disease except during muscle cramps In cases in which the disease is advanced movements of affected muscles may produce considerable pain There is no fever In cases which have been reported the ages of the patients have varied from nine months to forty eight years Electric reaction is diminished or absent Until the disease is well advanced the diagnosis cannot be made definitely without a biopsy

Prognosis.—The course of generalized myositis may be rapid and last only a few months or it may be very slowly progressive as in the case reported by Burton Cowan and Fleming in which the patient was still physically active after having had the disease ten years

Treatment.—Specific treatment is unknown Massage and electric treatment may relieve symptoms somewhat Drugs are of little help

Trichinous Myositis (Trichiniasis).—This is a myositis resulting from the invasion of voluntary muscles by *Trichinella* Trichinellae have been recovered from the diaphragm in from 3.5 to 27.6 per cent of cases at necropsy The condition is only recognized in cases in which the infestation is severe and associated with diarrhea acutely painful muscles edema of the muscles and subcutaneous tissues and eosinophilia Further details will be found in the section on Trichiniasis

CHARLES H SLOCUMB

MYOPATHIES

Myopathies include the diseases which are regarded as primary diseases of muscles but which are associated with secondary changes in the somatic nervous system The relation between the myopathies and the autonomic nervous system is not understood A consideration of the myopathies will be found elsewhere

CHARLES H SLOCUMB

INTERSTITIAL MYOSITIS

MYOSITIS OSSIFICANS

There are three types of myositis ossificans namely progressive circumscribed, and traumatic The traumatic type is associated with the formation of bone in a traumatized region Myositis ossificans circumscripta is usually associated with the formation of bone in a scar The progressive form will be considered more in detail

Progressive Myositis Ossificans.—Progressive myositis ossificans is a disease of unknown etiology which is characterized by proliferative inflammation in portions of the fibrous tissue of muscles tendons aponeuroses fasciae and ligaments It progresses to the formation of bone which eventually leads to destruction of the involved muscles and ankyloses of adjacent joints

Etiology and Incidence.—The etiology is unknown In 102 of 112 cases collected by Nutt the disease started before the age of

ten years It can start later in life, however Males are more frequently affected than are females Microdactylia of the thumbs or great toes, and occasionally of other toes or fingers, is an accompaniment in most of the cases

Morbid Anatomy—Rosenstirn and Mair regard the inflammation as a fibrositis rather than a parenchymatous myositis, hence it is here listed under interstitial myositis Three stages have been recognized Swelling edema and hemorrhage in the fibrous tissue in and around the involved muscles and proliferation of fibrous tissue are present in the first stage The skin and subcutaneous tissue may appear normal or may be swollen and red In the second stage the newly formed fibrous tissue contracts and forms a firm mass Bundles of muscle fibers are caught in the fibrous tissue and undergo degeneration In the fibrous tissue there appear cells resembling cartilage and clefts which resemble osteoid trabeculae and contain cells which later become osteoblasts and bone corpuscles When calcification occurs the parts enclosed by trabeculae form bone marrow In the third stage ossification occurs The new bone has been regarded as chemically and structurally the same as normal bone No abnormalities have been found in studies of the chemical constituents of the blood Wilkins Regen and Carpenter reported that the phosphatase activity of muscles in the preossification stage was 800 to 1600 times that of normal muscle and several times that of normal bone that of the heterotopic bone was much greater than that of normal bone

Symptoms—Progressive myositis ossificans may be present for years before it is recognized that limitations in the movements of certain muscles or joints are the result of bony deposits in muscle It may start as a soft doughy swelling in a muscle usually of the neck or back There may or may not have been an antecedent trauma Fever local tenderness and pain and edema and redness of the overlying skin and subcutaneous tissues may or may not be present After a few days the edema disappears leaving a firm nodule Other similar nodules may develop in adjacent muscles and fibrous tissues These firm nodules usually increase in size for a variable period and then regress but they seldom disappear completely Within about two to eight months deposits of bone in the involved regions can often be demonstrated by roentgenograms or by palpating a hard bony mass When the disease is extensive the deformities that develop usually stiffen the spinal column in the position of kyphosis, the scapulae are attached to the thorax by bony ridges which limit movements of the shoulders, the neck is rigidly anteflexed, and the arms legs and jaws may become ankylosed Amenorrhea and atrophy of the testes and scrotum have been noted in some cases

Diagnosis—The diagnosis is not difficult in advanced cases In early cases the early onset of swelling in the muscles, gradual progression of the disease, microdactylia and formation of hard masses in muscles and fibrous tissue should make one suspect the diagnosis which may be confirmed by roentgenographic examination or by microscopic evidence of the bone deposited in muscles Myositis ossificans traumatica and myositis ossificans circumscripta are distinguished from the progressive form by the absence of progression to other regions the presence of the ossification in injured regions or in regions in which a scar is present or an incision has been made Spondylitis deformans can be readily distinguished from progressive myositis ossificans, in cases of spondylitis there is generally early roentgenographic evidence of arthritis of the sacro iliac joints and there is an absence of the formation of bone in muscles

Prognosis—The disease may progress with remissions and exacerbations but the tendency is for the inflammation to spread progressively and irregularly into surrounding muscles fibrous tissue and bones producing destruction of muscles limitation of movements of joints and ankyloses Exostoses develop especially over fibrous and tendinous attachments to bones Death usually results from intercurrent infection from edema of the glottis or from suffocation as a result of limitation of costal breathing

Treatment—No medical treatment has been of help Excision of the bony deposits is sometimes advised in cases in which localized ossification interferes with function of the joints but this procedure is useless in cases of generalized myositis ossificans

surgical removal of new bone may be followed by the formation of more bone in the same region Protection against cold and dampness may prevent some exacerbations

CHARLES H SLOCUMB

INTRAMUSCULAR FIBROSITIS

Intramuscular fibrositis may be primary or secondary Primary intramuscular fibrositis is unaccompanied by and independent of any other recognized disease It is presumably attributable to an unidentified infection or toxemia Secondary intramuscular fibrositis is incidental or secondary to some known general infection or dominant primary condition such as rheumatic fever gout gonorrhea rheumatoid (atrophic) arthritis trauma and so forth

Secondary Intramuscular Fibrositis.—Secondary intramuscular fibrositis is likely to be disregarded in many cases or lost sight of while attention is paid to more painful symptoms Thus in acute rheumatic fever no special attention may be paid to muscles because during the active phase of the disease articular or cardiac symptoms may dominate and during convalescence the muscular symptoms may disappear rapidly Secondary intramuscular fibrositis is commonly associated with senescent (hypertrophic) arthritis but is most frequently encountered as a part of the syndrome of rheumatoid (atrophic) arthritis In the early stages of the latter disease the secondary fibrositis may for a while at least provide the chief symptomatic features Secondary fibrositis is frequently encountered in cases of gout and gonorrhea in which diseases one frequently encounters involvement of muscles but more particularly involvement of muscle tendons such as the Achilles tendons

The treatment of secondary intramuscular (or tendinous) fibrositis is chiefly that of the dominant disease of which the fibrositis is but a part

Primary Intramuscular Fibrositis (Muscular Rheumatism).—Primary intramuscular fibrositis may exist alone It is generally associated however at some time or other with other anatomic forms of primary fibrositis chiefly with tendinous fibrositis or periarticular fibrositis Of 100 cases of primary fibrositis studied by Slocumb twenty five were cases of primary intramuscular fibrositis alone twenty five were cases of primary periarticular fibrositis alone (without muscular symptoms) and fifty were cases in which symptoms of both intramuscular and periarticular fibrositis were present Primary intramuscular fibrositis will therefore, be considered further under the general consideration Primary Fibrositis '

CHARLES H SLOCUMB

PRIMARY FIBROSITIS

Primary fibrositis is a nonsuppurative inflammation of fibrous tissue anywhere in the body and is unrelated to any known disease. It has an acute subacute or chronic onset and course and produces minimal systemic reactions It may result in complete recovery or may become chronic with the production of long-continued aching and subjective stiffness

Etiology.—The etiology is unknown However many patients notice a direct relation between exacerbations of muscular symptoms and infections of the upper part of the respiratory tract influenza exposure to damp or cold weather fatigue and over exertion Some physicians regard infected foci constipation and colitis of importance in causing fibrositis Either sex and any age group may be affected Coates and Delicati (1932) reported that 25 per cent of the patients at a hospital for rheumatic diseases in Bath England were there for the treatment of fibrositis

Morbid Anatomy.—The pathologic reaction consists of an inflammatory hyperplasia of white fibrous tissue anywhere in the body that is in fasciae aponeuroses sheaths of muscles and nerves tendons ligaments articular capsules subcutaneous tissue and periosteum There are available very little data on the inflammatory reaction as it affects muscles or articular capsules Stockman who has made the most thorough study of the changes which take place in this disease confined his study to the histopathologic appearance of localized nodules and indurated regions Three types of nod

ing and arthritis of the hip occasionally must be excluded

Panniculitis —Panniculitis is fibrositis of the subcutaneous tissue The subcutaneous fat is separated by coarse bands of fibrous tissue and is tender to pressure Ecchymosis in the skin and subcutaneous tissues appears after minor trauma Fatigue and aching are the usual symptoms associated with panniculitis

Primary Fibrositis of Aponeuroses and Tendons —This generally is associated with other anatomic types of fibrositis There is local tenderness over the affected regions and tender nodules may be palpable Symptoms are usually aggravated by local pressure and by overuse of the affected part Favorite sites of involvement are the scalp especially the occipital region (indurative headaches) and lumbar region where the primary fibrositis of the aponeurosis is associated with intramuscular fibrositis

Primary Fibrositis of the Subacromial Bursa (Subdeltoid Bursitis, Periarthritis of the Shoulder) —This is an inflammation of the subacromial bursa adjacent tendons or capsule of the shoulder joint If the bursitis' is severe limitation of movement and pain are most noticeable when the shoulder is abducted or rotated internally Pressure over the bursa may cause pain The onset may be acute or insidious The condition may have been present for a few days or several months

Differential Diagnosis —Primary fibrositis of the shoulder is only one of several causes of subacromial bursitis and the condition cannot be diagnosed as primary fibrositis with reasonable certainty without evidence of primary fibrositis elsewhere Partial or complete rupture of the tendons of the supraspinatus infraspinatus biceps or teres muscles is distinguished from primary fibrositis of the shoulder by its association with strain or trauma, by roentgenographic evidence of atrophy of the humerus at the point of attachment of the affected tendons by reference of the pain into the muscles attached to the affected *tendons and into the* arm and by the absence of fibrositis elsewhere in the body Deposits of calcium in the tendons around the shoulder can be excluded by roentgenographic examination Necrosis in the tendons of the shoulder and serofibrinous subacromial bursitis, which have been described by Codman and by Dickson and Crosby are difficult to diagnose but are not associated with fibrositis elsewhere in the body Rheumatoid arthritis of the shoulder can be distinguished from primary fibrositis of the shoulder by the evidences of rheumatoid arthritis elsewhere in the body

Special Form of Primary Fibrositis, Jaccoud's Rheumatisme Fibreux —A form of severe chronic progressive fibrositis has been described by Jaccoud and others and has been given the name chronic rheumatisme fibreux' It is characterized by an abrupt or slow onset and course by the presence of swelling, tenderness and pain over the involved fibrous tissue of the tendons muscles and joints and by atrophy of the muscles The reaction in the synovial membrane is slight or absent Fibrous contractures produce articular deformities Jaccoud s disease may be a separate disease from primary fibrositis it may be a severe form of primary fibrositis or, as Stockman has suggested it may be an atypical rheumatoid arthritis

Prognosis —Acute attacks of primary fibrositis usually may last a few days or weeks but may recur Chronic primary intramuscular and periarticular fibrositis may persist for years but the patients are usually able to continue their work with only slight inconvenience Seldom is there sufficient contracture of fibrous tissue in periarticular and fascial fibrositis to limit the movement of joints however primary fibrositis of the palmar fascia occasionally produces a Dupuytren s contracture and primary fibrositis of the shoulder may limit the movement of the joint if systematic exercises are not practiced Most patients who have chronic primary fibrositis obtain considerable relief with treatment

Treatment —When an acute attack of primary fibrositis occurs the affected part should be rested protected from cold and kept warm Acetylsalicyclic acid in doses of *10 to 15 grains (0 6–1 Gm)* usually produces partial relief Counterirritants over the involved regions help to control the pain in severe cases *An acute attack* may sometimes be shortened by intravenous injections of typhoid vaccine in sufficiently large doses

to produce a fever of 101° to 103° F A cathartic should be given if the patient is constipated As soon as the acuteness of the attack is over the applications of heat should be followed by massage with firm pressure over the tender regions A careful search should be made for foci of infection especially in the teeth, tonsils prostate gland and uterine cervix In chronic primary fibrositis daily applications of heat should be followed by firm massage over the tender nodules and tender regions Firm massage may cause a transitory increase in pain for a few hours after the treatment but within two to ten days the patients will often notice definite improvement Treatment of infected foci protection against respiratory infections against chilling, dampness or sudden changes in temperature are important For fibrositis of the subdeltoid bursa and tendons of the shoulder local roentgen ray treatments may control an acute attack Subdeltoid bursitis resistant to conservative treatment may warrant a local injection of 3 to 10 cc of 0.5 per cent to 1 per cent novocain into the subdeltoid bursa

Charles H Slocumb

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DISEASES OF THE JOINTS

ARTHRITIS

Arthritis occurs in a number of different forms depending on various etiologic agents Some of these groups are characterized by certain pathologic and clinical features which make their differentiation comparatively easy In other instances only the most careful study will determine the etiology

Arthritis may occur in either an acute or chronic form However almost any type of acute arthritis may pass into a subacute or chronic form, and many cases of chronic arthritis are subject to acute exacerbations

The crucial point to determine in any case of arthritis is whether it is infectious or noninfectious in character Once this point has been settled a long step in advance will have been made in the handling of the case

The following classification of diseases involving the joints has been recommended by the New York City Committee on Arthritis Clinics

Classification of Diseases Involving the Joints

A Infectional arthritis of proved etiology
B *Probably infectional etiology unproved*
  1 Arthritis of rheumatic fever
  2 Rheumatoid arthritis (atrophic arthritis chronic infectious arthritis)
    (a) Adult type
    (b) Juvenile type (Still's disease)
    (c) Ankylosing spondylitis (Marie Strümpell)
    (d) Psoriatic arthritis
  3 Arthritis associated with various infections

C Degenerative joint disease
 1 Osteo arthritis (hypertrophic arthritis degenerative arthritis osteo arthrosis)
  (a) Generalized
  (b) Localized
   1 Secondary to previous trauma
   2 Secondary to structural abnormality
   3 Secondary to previous infectional arthritis
   4 Cause unknown
D Arthritis associated with disturbance of metabolism
 1 Gout
 2 Arthritic manifestations of other metabolic diseases
E Arthritis of neuropathic *origin*
 1 Secondary to tabes dorsalis
 2 Secondary to syringomyelia
F Neoplasms of joints
 (Cyst xanthoma hemangioma giant-celled tumors synovioma)
G Mechanical derangements of joints
 1 Traumatic arthritis
 2 Joint disturbance secondary to abnormal postural strain
H *Miscellaneous forms*
 1 Manifestations of systemic disease
  (a) Arthritis of serum sickness
  (b) Arthritis of hemophilia
  (c) Intermittent hydrarthrosis
  (d) Pulmonary osteoarthropathy
  (e) Hysterical joints
 2 Local joint disturbances
  (a) Aseptic bone necrosis
   1 Secondary to contusion fracture dislocation or air embolism
   2 Of unknown etiology (Juvenile osteochondritis Legg Calve Perthes disease Kohler's disease Freiberg's disease Osgood Schlatter's disease)
  (b) Osteochondritis dissecans
  (c) Osteochondromatosis

RUSSELL L CECIL

INFECTIONAL ARTHRITIS OF KNOWN ETIOLOGY

Gonococcal Arthritis—Gonococcal arthritis is an acute inflammation of a joint caused by the gonococcus Gonococcal arthritis has been described in full in the section on Gonococcal Infections page 166

Pneumococcal Arthritis—Pneumococcal arthritis usually occurs as a complication of lobar pneumonia although occasionally cases are seen in which it is secondary to some other primary focus

The majority of cases occur in children or young people The incidence of pneumococcal arthritis in pneumonia varies from 0 5 to 1 per cent In cases not associated with pneumonia most of the patients give a preceding history of tonsillitis otitis sinusitis or some other such focus of pneumococcal origin

Pneumococcal arthritis is usually monarticular, though it may occur in a polyarticular form as well The large joints are usually affected, and the condition is seen in all grades of severity In the milder cases there is nothing more than a serous effusion into the joint and a mild degree of periarticular inflammation which clears up spontaneously In the majority of cases however the process goes on to suppuration with partial or complete erosion of the cartilage

Pneumococcal arthritis should be strongly suspected in any patient who in the course of lobar pneumonia develops an acutely swollen joint In every case however the final diagnosis must depend upon joint puncture and the demonstration of pneumococci in the fluid

Very mild cases will clear up spontaneously Others will be relieved by sulfonamides or by aspiration and irrigation with some germicidal solution If joint puncture reveals frank pus surgical measures are necessary

Suppurative Arthritis—Suppurative arthritis or surgical joint ' may occur at any age but is particularly common in children It is usually caused by the *Streptococcus haemolyticus* or the *Staphylococcus aureus*

In suppurative arthritis infection of the joint may follow a penetrating wound of the joint or may develop *as a secondary* complication in a patient with bacteremia Occasionally the arthritis is secondary to an adjacent osteomyelitis which involves one of the bones entering into the formation of the joint By far the largest number are secondary to some form of bacteremia, the original focus being a furuncle, an infected wound a mastoid infection or some other localized inflammatory focus

Like most joint infections suppurative arthritis starts in the synovial membrane This rapidly becomes swollen and inflamed, and an exudate rich in polymorphonuclear leukocytes forms in the joint cavity and soon takes on the properties of pus Many of the patients give a history of trauma to the affected joint a day or two after which there is sudden pain and swelling in the joint and excessive pain on movement

There may be an initial chill and a rise in temperature to 102° or 103° F. The joint is hot, swollen and tender and in a short time fluctuation is present.

Aspiration of the joint reveals purulent fluid, cultures from which usually show streptococci or staphylococci.

The treatment is always surgical.

Syphilitic Arthritis.—Syphilis may manifest itself in the joints during either the secondary or the tertiary stages of the disease.

The arthritis of *secondary syphilis* is associated with the other symptoms of secondary lues and is characterized by swelling, tenderness and limitation of motion of several of the larger joints.

The arthritis of *tertiary syphilis* is usually monarticular. It develops late in the disease and is characterized by gummatous thickening of the synovial membrane and capsule. Clinically this form of arthritis runs a chronic course similar in many respects to tuberculous arthritis. There is considerable swelling but no redness, and fluctuation is usually demonstrable. The knee is particularly prone to involvement. Chesney, Kemp and Baetjer state that hydrops of the knee joint associated with periostitis immediately adjacent to the joint is strongly suggestive of syphilis, especially when the patient gives no history of trauma.

The treatment of luetic arthritis is that of syphilis elsewhere in the body. In a case which has not been too long neglected, specific treatment usually yields excellent results.

Tuberculous Arthritis.—Tuberculous arthritis occurs most frequently in children. It is usually monarticular. Almost any joint in the body may be involved, but tuberculosis of the hip joint and tuberculosis of the spine are the two most common forms.

The treatment of tuberculous arthritis is largely surgical and orthopedic. For a full discussion of tuberculous arthritis the reader is referred to any standard treatise on surgery or orthopedics.

Other Forms of Infectional Arthritis.—In addition to the common forms of infectional arthritis already described, other bacteria occasionally localize in the joints and set up inflammation. Among these may be mentioned:

1. *The Arthritis of Scarlet Fever.*—This occurs in two types: (*a*) so-called 'scarlatinal rheumatism'; (*b*) septic arthritis caused by the *Streptococcus haemolyticus* and differing in no respect from the ordinary surgical joint.

2. *The arthritis of cerebrospinal fever*, which also occurs in two forms, one resembling rheumatic fever and usually running a transitory course, the other a true meningococcal infection of the joint and characterized by the formation of a seropurulent exudate rich in pus cells and meningococci.

3. *The Arthritis of Influenza.*—Several cases of influenzal arthritis, monarticular in type, have been reported. Most cases have occurred in children. The affected joint contains a seropurulent fluid, cultures from which yield *Hemophilus influenzae*.

4. *The Arthritis of Puerperal Fever.*—In many patients with puerperal fever, the *Streptococcus haemolyticus* can be isolated from the blood. When this organism localizes in the joint, a suppurative arthritis develops.

5. *The Arthritis of Brucellosis.*—Arthritis is a frequent and characteristic symptom of brucellosis. Several of the large joints are usually affected, and the acute manifestations migrate from joint to joint. Eventually the joints clear up spontaneously.

6. *The Arthritis of Subacute Bacterial Endocarditis.*—In the course of this disease the patient may complain of pain and stiffness in some of the joints. This may be fleeting and of a mild character, or the joints may be swollen and red and the symptoms persist for some time. The symptoms suggest a mild form of rheumatic fever. The treatment is that of bacterial endocarditis and is entirely symptomatic.

7. *The Arthritis of Typhoid Fever.*—Typhoid arthritis is a rare condition and has already been described in the section on Typhoid Fever, page 199.

8. *The Arthritis of Bacillary Dysentery.*—Arthritis is one of the commonest complications of bacillary dysentery and usually affects the knee, though other joints may be involved. It develops after the acute stage of dysentery is over and is accompanied by a recrudescence of fever and serous effusion into the joint.

RUSSELL L. CECIL

THE ARTHRITIS OF RHEUMATIC FEVER

Rheumatic fever is a generalized infection characterized in most instances by acute inflammation of the joints Rheumatic fever is described in detail on page 435

RHEUMATOID ARTHRITIS

(*Chronic Infectious Arthritis Atrophic Arthritis Arthritis Deformans*)

Definition—Rheumatoid arthritis is a chronic disease of the joints characterized by inflammatory changes in the synovial membrane and periarticular structures, and by atrophy and rarefaction of the bones In the earlier stages the disease manifests itself as a migratory swelling and stiffness of the joints, in the later stages by more or less deformity and ankylosis

Incidence—Unfortunately we have no accurate figures concerning the incidence of rheumatoid arthritis It is known however to be quite prevalent in the temperate zone and almost unknown in the tropics It is fairly common in the southern portion of the United States Dawson points out that a large proportion of cases observed in New York City have their onset in the spring months particularly the month of March Rheumatoid arthritis is three times as common in females as in males It is essentially a disease of young people the average age of onset being thirty five years

Etiology—The etiology of rheumatoid arthritis has not been finally determined In spite however, of the lack of knowledge concerning the exact cause of the disease there are certain predisposing factors which are universally accepted as being conducive to its development

Predisposing Causes—Among the more important predisposing factors may be mentioned

SHOCK—A severe physical or emotional shock often precedes the onset of rheumatoid arthritis A death in the family a difficult labor, a surgical operation or some business calamity is often mentioned as having occurred just before arthritis developed

FATIGUE—Fatigue, either mental or physical is another important predisposing cause

TRAUMA—Infectious arthritis frequently makes its first appearance in a joint which has previously been the seat of trauma A sprained ankle, a fracture or a gunshot wound lowers the local resistance, and the rheumatoid process is initiated at this particular point The disease may occasionally remain localized in one joint, but more frequently other joints subsequently become involved It has been shown experimentally in rabbits that when a joint is injured and streptococci are then injected into the blood stream the bacteria show a strong predilection for the injured tissue

INFECTIONS—Rheumatoid arthritis occasionally makes its first appearance shortly after an acute infection particularly the more common ones such as acute coryza tonsillitis sinus infection influenza pneumonia or typhoid fever

EXPOSURE—Sudden or repeated exposure to dampness rain and cold is one of the commonest predisposing causes of rheumatoid arthritis This was well shown by Pemberton in his statistical study of arthritis in soldiers A high percentage of the men who developed chronic arthritis gave a definite history of standing in water, marching or sleeping in the rain, or of prolonged exposure to cold weather

CONSTITUTIONAL INFERIORITY—Osgood has stressed the high incidence of rheumatoid arthritis in the thin visceroptotic type of individual The muscles are poor the thoracic cage is narrow the chest expansion small, the weight bearing lines of the joints are not true and because of poor muscle tone the patient is easily fatigued

HEREDITY—Rheumatoid arthritis is said to run in families The writer has been rather impressed with the frequent tendency of the disease to develop in the offspring of arthritic patients

CLIMATE—Rheumatoid arthritis is a disease of the temperate zones It is rarely encountered in the tropics

Exciting Causes—The exciting cause of rheumatoid arthritis is still very much under debate The fundamental question is is rheumatoid arthritis an infectious disease? Most students of the disease accept the infectious theory although there are some who still do not The evidence in support of the infectious theory is considerable The

clinical course of rheumatoid arthritis is strongly suggestive of an infectious disease and the lesions in the joints are essentially inflammatory similar in many respects to those in other well known infections of the joints

In 1912 Billings and his co workers first called attention to focal infection as an etiologic factor in chronic arthritis These foci were found most frequently in the tonsils or sinuses or at the roots of devitalized teeth At times foci of infection were also found in other parts of the body such as the gall bladder or genito urinary tract During the thirty years which have elapsed since the publication of Billings' article focal infection has come to occupy a very important place in the activities of medical and surgical practice especially in relation to the various forms of arthritis and rheumatism However *in a recent study reported by* Cecil and Angevine on 200 cases of rheumatoid arthritis definite evidence of focal infection was present in only 20 per cent of the cases and careful investigation revealed that removal of foci either before or after the patient came under observation, rarely produced any permanent benefit on the course of the disease At the present time there is a feeling among students of arthritis that the theory of focal infection has been overstressed in the etiology of rheumatoid arthritis and the author concurs in this view One thing seems to be quite certain and that is that foci of infection are not any more frequently encountered in rheumatoid arthritis than they are in other diseases or in healthy individuals

Bacteriology—Considerable research has been directed toward the bacteriology of rheumatoid arthritis but little of it has thrown much light on the real nature of the condition *The frequent presence of strepto*cocci in the various infections which are sometimes associated with arthritis has naturally focused the interest of bacteriologists on this micro organism and a number of investigators have reported the isolation of streptococci from both the blood and joints of patients with rheumatoid arthritis the percentage of positive results varying widely in different studies Carefully controlled studies have seemed to indicate that in the great majority of cases the streptococci which have been recovered from the blood and joints of rheumatoid patients are accidental contaminations

Agglutination and Precipitation Reactions—Agglutinins for the *Streptococcus haemolyticus* were first demonstrated in the serums of patients with rheumatoid arthritis in 1931 by Cecil Nicholls and Stainsby, who showed that most of the attenuated hemolytic strains recovered from arthritic patients were agglutinable with rheumatoid serum even in very high dilutions Nicholls and Stainsby noted that hemolytic streptococci from other sources such as scarlet fever and erysipelas were often agglutinable with arthritic serum These results have been confirmed by numerous observers It has also been found that the serums of patients with rheumatoid arthritis frequently give a positive precipitation reaction with the *protein fractions of S haemolyticus*

Experimental Arthritis—When strains of streptococci which have been isolated from patients with rheumatoid arthritis are injected into rabbits a large proportion of them develop signs of arthritis in one or more joints If repeated intravenous injections of streptococci are made a chronic progressive arthritis often develops The condition then resembles the rheumatoid arthritis of man Indeed microscopic sections from the two conditions are hardly distinguishable In rabbits with experimental streptococcus arthritis the streptococci can often be recovered from the blood stream and from the affected joints and the blood of the arthritic rabbit shows high agglutinins for the homologous streptococci Sabin has produced a subacute proliferative polyarthritis in mice by the intravenous injection of a filtrable micro organism of the pleuropneumonia like group

In conclusion it must be admitted that the etiology of rheumatoid arthritis has not yet been determined The disease certainly presents the picture of a chronic low grade infection and there is a certain amount of evidence that it is of streptococcal origin however the proof of this theory is still lacking

Morbid Anatomy—The tissue changes which take place in rheumatoid arthritis proceed in a certain sequence In the early stages *swelling of the joint is* the most char

acteristic feature This swelling is due to active inflammation in the various parts of the joint, particularly in the synovial membrane, the capsule and the surrounding soft tissue The synovial membrane is swollen and deep red in color and the villous processes show marked hypertrophy In advanced cases, granulation tissue extends over the articular surfaces of the joint in the form of a pannus which eventually is converted into dense fibrous tissue This binds the two contiguous articulating surfaces together in fibrous ankylosis In other *instances ankylosis does not occur but the* cartilage ulcerates and there is an increase of fluid in the joint cavity Finally, subluxations and distortions of the affected joints lead to deformities so characteristic of the disease

In addition to the destructive changes in the joint itself a certain amount of atrophy occurs in the long bones in the muscles and in the skin In an advanced case of rheumatoid arthritis the bones are smaller and more brittle than normal the muscles show marked wasting and the skin over the affected parts is thin tight and glossy

Microscopically the histologic changes in the joints are those of a chronic infectious process In a section taken through the synovial membrane the surface is often found covered with a thin layer of necrotic material densely infiltrated with leukocytes, beneath which there is vascular granulation tissue rich in fibroblasts monocytes and leukocytes of various kinds

Allison and Ghormley maintain that rheumatoid arthritis has a specific micropathology In addition to the chronic granulation tissue which occurs in the synovial membrane and which in itself is rather characteristic there is a more specific lesion consisting of peculiar clumps of lymphoid cells, which they claim are not encountered in other forms of chronic *arthritis*

Perhaps the most interesting pathologic lesion in rheumatoid arthritis is the subcutaneous nodule which occurs in about 10 per cent of the cases Microscopic sections of these nodules show small granulomatous foci somewhat suggestive of miliary tubercles, which consist of an area of central necrosis surrounded by a zone of large mononuclear cells arranged in characteristic radial fashion, and an enveloping area of dense fibrous connective tissue McEwen has shown that these cells are of the same type as *those which occur* in the granulomata of rheumatic fever and that they are quite distinct from the epithelioid cells of tuberculosis and syphilis The changes in the heart are usually insignificant except in those cases of rheumatoid arthritis in which there is a history of rheumatic fever In such cases the various lesions characteristic of rheumatic fever may be found on the valves or in the heart muscle.

Physiology—*There are surprisingly few* chemical changes in the blood of arthritic patients Pemberton and Foster have shown that the blood urea and the nonprotein nitrogen are well within normal figures The *same authors estimated* the carbon dioxide combining power for blood the calcium of the circulating blood and the total fat and cholesterol of the fasting blood in arthritics and in all cases found the figures within normal limits

Pemberton and Foster reported a diminished sugar tolerance in rheumatoid arthritis Their observations were supported by the investigations of Fletcher who found a diminished sugar tolerance in a large majority of cases of rheumatoid arthritis Bauer has found that the delayed rate of sugar removal is secondary to circulatory changes

The basal metabolism in rheumatoid arthritis is close to the average normal level The respiratory quotient is also *normal and* there is no evidence of abnormal respiratory metabolism following the ingestion of large test meals of glucose and protein The calcium and phosphorus metabolism are both normal in rheumatoid arthritis

Symptoms—The patient with rheumatoid arthritis can often date the onset of symptoms from some disturbance of his physical equilibrium such as an acute in*fection exposure to cold* a surgical operation fatigue from overwork or an emotional strain Certain prodromal symptoms may first be noted the more common of which are weakness and fatigue loss of weight, anemia and vasomotor disturbances particularly tingling and numbness in *the hands* and feet The onset may be sudden or gradual When the onset is acute the pain and swelling of the joints come on rapidly and

are associated with chills fever prostration and other features of acute infection but in a great majority of cases the disease makes its appearance very insidiously

When the onset is gradual symptoms usually appear first in only one joint Often *there is pain and stiffness in this particular* joint for weeks or even months before other joints are affected Very gradually the joint begins to swell The temperature is normal or only slightly elevated often running for weeks from 99° to 100° F The pulse is somewhat accelerated and even early in the disease there may be some anemia

Regardless of whether the symptoms develop suddenly or gradually the disease eventually assumes a chronic course The constant involvement of the adjacent nerves

In the majority of patients the hands are sooner or later involved and present a characteristic appearance In the fingers one sees the badge of the disease a pod shaped swelling *of the proximal interphalangeal joint*, the so called fusiform or sausage finger The distal interphalangeal joints are rarely involved As the disease progresses many or all of the fingers may be implicated and swelling appears in the knuckles and wrists The knees are nearly always affected and usually early in the disease The joint becomes *swollen warm* and contains a moderate excess of fluid There is considerable tenderness on pressure and flexion is painful

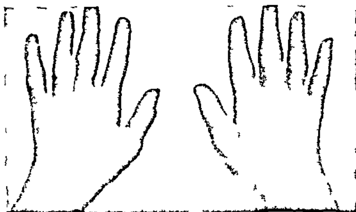


Fig 177—Hands of a young woman with early rheumatoid arthritis showing typical fusiform swelling of the proximal interphalangeal joints Notice the symmetric distribution of the joint swelling (From Oxford Monograph, Cecil s Diagnosis and Treatment of Arthritis courtesy of the Editor Dr Henry A Christian and Oxford University Press)

characteristic features of rheumatoid arthritis are the swelling of the joints particularly those of the fingers hands and knees the symmetrical distribution of the arthritic manifestations the migratory character of the joint *symptoms especially in the early* stages the tendency of the disease to progress into a chronic state and the eventual ankylosis and deformity of the joints if the disease is not arrested

The degree of pain in the affected joints varies considerably and is not entirely proportional to the amount of swelling in the joint With many of these patients there is comparatively little pain except with exercise Arthritis of the hip and of the spine are perhaps the two most painful forms of the disease probably because of the almost and limited The ankles are frequently affected but the toes are often spared possibly because they are subject to so little exercise The temporomandibular joint is more frequently involved in rheumatoid arthritis than in *any other form of joint* disease and causes the patient considerable pain and discomfort when the jaw is exercised

As the disease progresses flexion deformities take place in the elbows and knees as well as in the fingers and wrists At first these muscle spasms can be overcome under anesthesia but as time goes on the joints become fixed in this position and extension becomes more and more difficult Marked muscular atrophy and wasting lead to still more deformities and subluxations In the

hands lateral deflection and subluxation at the metacarpophalangeal joints produces the characteristic ulnar deviation which is one of the earmarks of the disease

The heart is rarely affected in rheumatoid arthritis In those cases where valvular dis ease is present the patient usually gives a history of a preceding rheumatic fever The pulse rate is usually accelerated running between 90 and 100

Among the most remarkable accompani ments of rheumatoid arthritis are the so called 'subcutaneous nodules' which occur in 10 per cent of all cases They are usually found about the elbows wrists or fingers occasionally over the ankles and appear as hard movable nodules which vary in size from that of a pea to that of a walnut They may disappear in a short time or persist for months Iritis is a rather rare complication

Physical Signs —The typical arthritic presents certain *constitutional signs that are* striking These patients are usually anemic averaging about 70 per cent of hemoglobin many of them appear chronically ill and undernourished some are markedly emaci ated, particularly those in whom the disease has lasted for some time A few patients however show excellent nutrition and no anemia

Examination of the tonsils *may show* chronic infection The gums may be the seat of various *grades of gingivitis or pyorrhea* Transillumination of sinuses may reveal a chronic sinusitis In the experience of the writer however the demonstration of frank focal infection is an unusual experience in these patients and certainly no more prev alent than in patients suffering from other ailments

In the early stages the joints affected usu ally present a characteristic appearance There is more or less swelling of the soft parts and the overlying skin is warm and sometimes reddened In some cases there is an increase in synovial fluid The swelling is due for the most part to the outpouring of inflammatory exudate into the periarticu lar structures Tenderness is *usually present* and is most marked on the lateral aspects of the joints Motion either active or passive is painful In the early stages of the disease *there is no crepitation*

In the later stages some of the swelling may disappear but a certain amount of thickening persists about the joint due to a new growth of fibrous tissue in this region In the joint itself the *granulation tissue* may become converted into adhesions which eventually lead to partial or complete fibrous ankylosis In those cases in which *proliferation of the perichondrium* predomi



Fig 178—*Hands of an elderly man with advanced rheumatoid arthritis showing the characteristic deformities and ulnar deviation of fingers Most of the swelling has disappeared from the joints*

nates, bony ankylosis is apt to occur Ankylosis is usually associated with considerable atrophy of the neighboring muscles

The longer the duration of the disease the more frequently bony changes can be demonstrated in the joints In patients who are seen early there may be no swelling or bony changes present and the disease is manifested solely by subjective sensations of pain In these cases examination of the joint reveals nothing abnormal except possibly slight tenderness on pressure Fusiform finger joints are a common finding and when seen are almost pathognomonic The cold clammy hands of the rheumatoid patient are particularly characteristic

Clinical Course —When the onset of rheumatoid arthritis is acute the disease may run a comparatively short course with complete disappearance of symptoms The patient may then be entirely free from joint trouble for several months or even years In a majority of cases however the condition returns after a lapse of time and with each recurring attack takes on a more chronic course

In those cases where the onset is gradual the disease usually runs a chronic course extending over years There may be periods of comparative comfort alternating with periods of active advance With each exacerbation the joints become progressively stiffer and more permanently injured With loss of function muscular atrophy becomes more and more pronounced and flexion deformities especially in the elbows and knees make their appearance

If the process is checked in its early stages all of the symptoms of arthritis may disappear with complete return of normal function in the affected joints Even in well established cases recovery sometimes occurs either spontaneously or as a result of treatment. In such cases the patient may recover partial or complete use of the affected joints even where swelling and deformity do not entirely disappear If the disease is not checked the patient eventually becomes a bedridden cripple presenting a pitiful picture with his contracted deformed limbs and markedly wasted muscles

X Ray Findings —In the early stages of rheumatoid arthritis radiographs of the affected joints may be entirely negative Later on as the process advances there is haziness and narrowing of the interarticular space Still later in the disease as the inflammatory tissue destroys the cartilage the adjacent articular surfaces come into actual contact so that the two bones appear to be fused together At this stage there is considerable atrophy and rarefaction of the cancellous bone due to the diminished calcium content, and small areas of bone destruction frequently referred to as punched-out areas are often demonstrable These areas of erosion are smaller than those which occur in gout In the last stages of the disease when the bone itself is partially destroyed and ankylosis has occurred the markings of the joint are replaced completely by a diffuse shadow which merges with the adjacent bone. Late in the disease the bone may undergo some hypertrophic changes Such hypertrophy however is almost never seen in the early stages



Fig 1"9 —Rheumatoid arthritis in an elderly woman showing swelling and deformity of hands and large subcutaneous nodules near the elbows

Laboratory Findings —Secondary anemia sometimes of fairly severe grade is present in the majority of patients with rheumatoid arthritis

A moderate leukocytosis is found in a considerable number of rheumatoid patients

and the *Schilling hemogram frequently* shows increase of the immature cells, particularly in active cases

The sedimentation rate of the red blood cells is considerably increased in most cases In active cases it may be three or four times the normal rate

In 70 per cent of well established cases the patient s serum will give a positive agglutination reaction to the hemolytic streptococcus The albumin globulin ratio is increased in the great majority of cases

The urine shows no characteristic changes

Diagnosis —The diagnosis of a typical case of *rheumatoid arthritis* presents very little difficulty The important features in diagnosis are

1 Its tendency to occur in young adults, though it may occur at any age

5 In severe cases which are not checked more or less deformity and ankylosis eventually take place

Differential Diagnosis —The most important differential diagnosis is that between rheumatoid arthritis and hypertrophic or so-called ' degenerative arthritis In the latter type there is an absence of inflammatory swelling The disease does not spread but remains localized in a few joints In rheumatoid arthritis, there is a loss of calcium in the bone *which shows up in the x ray* the bone being much more transparent than normal In hypertrophic arthritis there is an increased amount of calcium deposit particularly around the joint which in the x ray appears as a condensation of the bone adjacent to the articular surface, and an actual new formation of bone around the margins of the joint The distinction between infectious arthritis and hypertrophic arthritis is very important as the line of treatment to be instituted is quite different *for the two groups*

DIFFERENTIAL DIAGNOSIS OF RHEUMATOID ARTHRITIS

	Rheumatoid Arthritis	Degenerative Arthritis
Average age of onset	Third and fourth decades	Fifth and sixth decades
Weight	Normal or underweight	Usually overweight
Condition of bones	Rarefaction	Condensation of articular margins
Joints involved	Any joint in body	Chiefly knees spine and fingers
Type	Migratory	Not migratory
Appearance of joints	Periarticular swelling	No swelling
Special signs	Fusiform finger joints	Heberden s nodes
Subcutaneous nodules	Present in 10 per cent of cases	Never present
Roentgen ray	Narrowing and clouding of joint space	Lipping of bony margins of joint
Streptococcal agglutinins	Usually present	Never present
Blood count	Secondary anemia and slight leukocytosis	Normal blood count
Sedimentation of R.B C	Considerably accelerated	Normal or slightly accelerated
Course	*Usually progressive*	*Stationary or slightly progressive*
Termination	*Ankylosis and deformity*	*No ankylosis usually no deformity*

2 The migratory character of the joint *symptoms is characteristic particularly in* the early stages Later on, the changes in the joints become chronic and persisting and tend to a *symmetrical distribution*

3 The affected joints usually are swollen and tender In mild cases there may be an entire absence of swelling but as a rule some degree of infiltration is present and one should hesitate to make a diagnosis of rheumatoid arthritis if no swollen joints are demonstrable

4 Rheumatoid arthritis is very prone to attack the metacarpophalangeal and proximal phalangeal joints with the production of fusiform fingers The tendency toward symmetrical distribution of the fusiform swelling of the fingers is quite characteristic

It must not be forgotten that in the case of a middle aged individual rheumatoid ar*thritis may be superimposed* on a degenerative arthritis and that both processes may attack the same joint

It is very easy to mistake gonococcal arthritis for rheumatoid arthritis especially in women who have no vaginal discharge *Gonorrheal arthritis is* polyarticular and the swollen painful joints may bear a close resemblance to those of rheumatoid arthritis *In this differentiation* the history is of great importance as well as the examination

of the genito urinary tract The gonococcus complement fixation test when properly performed is a valuable laboratory procedure and can usually be depended on especially when a strongly positive reaction is reported The agglutination reaction with the *Streptococcus haemolyticus* is also reliable in differentiating these two forms of arthritis The sedimentation rate is increased in both diseases

Rheumatoid arthritis must be differentiated from subacute rheumatic fever a distinction which is not always easy to make In both conditions the patient may give a history of a preceding tonsillitis followed by an acute arthritis with fever and swelling of the joints In rheumatic fever however the temperature is higher the sweating is more profuse and cardiac complications are quite frequent The therapeutic test is valuable Treatment with sodium salicylate or aspirin usually gives instant and permanent relief in rheumatic fever In rheumatoid arthritis these drugs produce only a temporary improvement

Luetic arthritis particularly that form associated with secondary lues might possibly be confused with infectious arthritis Careful examination however usually reveals other signs of syphilis

Tuberculous arthritis possibly might be mistaken for rheumatoid arthritis The former however is nearly always monarticular, the latter is usually polyarticular X ray examination will be of great assistance in making the distinction but in some cases it may be necessary to resort to exploration and animal inoculation A tuberculous or luetic joint is much more apt to present fluctuation than the joint of rheumatoid arthritis

Arthritis Associated with Focal Infections—Certain cases of infectional arthritis are definitely associated with local infection and are promptly relieved when the focus is removed Indeed these cases tend to recover completely whether or not the focus is removed Some writers believe that this type of arthritis should be classified as rheumatic fever or rheumatoid arthritis However there are certain differences which are worth mentioning Onset and exacerbations are closely associated with flare ups of the focus of infection Usually several of the large joints are affected There is considerable pain and some fever and leukocytosis

In differentiating rheumatoid arthritis from other chronic joint conditions the writer has obtained much help from some of the blood tests mentioned under laboratory findings The sedimentation rate and the Schilling count are both good indices of infection and are of assistance in separating infectious arthritis from the noninfectious forms The streptococcal agglutinin test with the patient s serum helps to distinguish infectious arthritis of the rheumatoid type from joint infections due to other bacteria



Fig 180—Radiograph of spine of a young man with advanced ankylosing spondylitis (Marie Strümpell spine) Notice how the bodies of the vertebrae are fused together by membrane of calcifying fibrous tissue The sacro-iliac joint markings have been obliterated

Other Forms of Rheumatoid Arthritis—*Still s Disease*—In 1897 Still described a form of polyarthritis in children and reported twelve cases of the disease Since then numerous additional cases have been observed The whole picture is that of a chronic infection, and most students of arthritis are disposed to look upon it as rheumatoid arthritis modified somewhat clinically by the age of the patient

So far as the morbid anatomy of the disease is concerned the findings in the joints are similar to those of rheumatoid arthritis In the later stages ankylosis and deformity

occur with marked atrophy of the muscles Lipping and spurring of the articular surfaces almost never occur, but considerable rarefaction of the bone is shown by x rays In addition to the changes in the joints hyperplasia of the lymph nodes and enlargement of the liver and spleen frequently occur Amyloid degeneration has been noted in the liver, spleen, lymph nodes and kidneys

Ankylosing Spondylitis —Most patients with rheumatoid arthritis sooner or later develop symptoms in some part of the spine particularly the cervical portion However there is a special form of infectional arthritis in which the entire spine may become implicated This may exist without involvement of other joints, and is then usually referred to as ankylosing or Marie Strumpell spondylitis (poker spine) Many students believe that this disease is entirely distinct from rheumatoid arthritis Certainly it differs fundamentally in one respect from rheumatoid arthritis in being a disease of men, mostly young men Typical Marie-Strumpell spines are rarely encountered in the female

Ankylosing spondylitis usually makes its first appearance in the lower back affecting first the sacro iliac and the lumbosacral joints The small articulations of the apophyseal and costovertebral joints are often affected The pathologic changes are similar to those which occur in the joints of patients with rheumatoid arthritis but in addition, the longitudinal ligaments show a marked tendency to become calcified As the disease progresses upward more and more of the vertebrae are involved until in advanced cases, complete ankylosis of the entire spine takes place

These young men present a very characteristic appearance The lumbar curve is flattened and the dorsal curve exaggerated The chest is flat and rigid and there is spasm of the deep back muscles The patient flexes the body at the hips the entire spine being held rigid and chest expansion is markedly curtailed These patients are usually very poorly nourished and there is marked atrophy of the trunk muscles In advanced cases the spinal column becomes fused into one piece which admits of no motion in any direction, and there is a tendency for the disease to extend into the shoulder and hip joints with eventual ankylosis in these joints also

Radiographs are very characteristic and establish the diagnosis Early cases may show no changes but in advanced cases there is demineralization of the bone obliteration of the small intervertebral articulations and calcification of the intervertebral ligaments (bamboo spine) The sacro iliac joints are affected in 90 per cent of the cases

Remarkable progress has been made in the treatment of ankylosing spondylitis since the discovery that this form of joint disease responds amazingly well particularly in the early stages to deep x ray therapy Cases so treated often make a complete and permanent recovery In the more advanced cases a certain amount of ankylosis persists but the pain disappears and as time goes on often the stiffness becomes less marked

Psoriatic Arthritis —Psoriatic arthritis or *psoriasis arthropathica* is frequently referred to in the literature on arthritis and is considered by some clinicians as a separate disease entity However the majority of these patients present the characteristic picture of rheumatoid arthritis According to Dawson 2 5 per cent of patients with rheumatoid arthritis are also the victims of psoriasis Psoriasis usually precedes the arthritis but the reverse may be true It is also interesting to note that remissions and exacerbations of arthritis are usually accompanied by remissions and exacerbations of the psoriasis

Prognosis —The prognosis in rheumatoid arthritis is dependent on many factors Perhaps the most important of these is the application of rational treatment early in the disease The prognosis is affected by the morale of the patient and by his constitutional make up Robust well developed individuals respond to treatment more readily than those with inferior physiques The actual number of patients who make a complete and permanent recovery is not accurately known So often the disease becomes arrested or quiescent only to flare up again later on when for some reason the patient's resistance has been lowered Patients who are running an acute febrile course appear to respond more quickly to

treatment than those who present a chronic indolent type of arthritis In the opinion of the writer the prognosis in early rheumatoid arthritis has definitely improved since the introduction of gold therapy

Rheumatoid arthritis alone is never a menace to life In advanced cases however where the patient s general health has undergone marked deterioration the danger of death from some intercurrent infection is quite real

The sedimentation rate of the red blood cells can be used with great advantage in following the rheumatoid patient to determine from time to time the activity of his infection We have also found that as the rheumatoid patient improves the amount of specific streptococcal agglutinin decreases in the blood and if recovery occurs the agglutinins disappear entirely

Prophylaxis —As long as the etiology of rheumatoid arthritis remains in doubt the prophylaxis of the disease will continue to present a difficult problem Obvious foci of infection should of course be removed but it is doubtful if this measure alone would prevent rheumatoid arthritis

One of the most striking features of rheumatoid arthritis is its tendency to relapse Many patients recover completely from the first attack of the disease and remain free from symptoms for several years The second attack is nearly always more stubborn in its course and often goes on into the chronic progressive form In view of this characteristic of the disease every effort should be made to prevent the second attack The patient s life and personal hygiene must be carefully regulated to a point well within his capacity to function without fatigue

Treatment —Rheumatoid arthritis is usually a chronic progressive disease similar in many respects to tuberculosis and syphilis Success in treatment therefore depends on the promptness and vigor with which it is instituted Unfortunately there is no specific therapy for rheumatoid arthritis The treatment resolves itself into efforts to increase the patient s resistance and to put him in the best possible health In addition to these general measures especial attention must be devoted to the inflamed joints to prevent ankylosis and deformity

Active incipient cases with fever can often be greatly benefited by four to six weeks intensive treatment in a hospital This will rarely be sufficient to produce a cure but the patient comes out feeling better and stronger and often afebrile He can then be treated at home or at the physician s office as seems desirable Even those patients with more advanced arthritis will often benefit considerably from a few weeks of hospital care A well equipped hospital not only provides complete rest and good nursing but offers facilities for fever therapy, physical therapy orthopedic treatment etc which are difficult to obtain at home Hospital care also offers opportunity for the investigation and removal of any possible source of infection

Rest —All students of rheumatoid arthritis are agreed that complete and prolonged rest is the keynote to successful treatment of this disease In many ambulant cases complete rest is a difficult form of therapy to enforce chiefly because the patient is anxious to keep up his daily duties However if these patients in the early stages of rheumatoid arthritis could be persuaded to give up work and take a rest cure for six months or a year a much higher percentage of them would make a complete and permanent recovery As it is and chiefly for economic reasons the physician must compromise on the rest issue and the patient is advised to take from one to two hours rest in bed every day after lunch If a real rest cure can be taken it is far preferable because the patient gets a mental and emotional rest as well as a physical one In well established cases rest in bed for a considerable part of the day is absolutely essential There should also be long sleeping hours at night induced by some mild hypnotic if necessary

Dietary and Vitamin Regime —No special diet is indicated in the treatment of rheumatoid arthritis Most rheumatoid patients are undernourished and underweight and one of the duties of the physician is to try to restore the lost weight by means of a nutritious well balanced diet In order to achieve this a high calory high vitamin diet rich in vegetables and fruits is indicated Pemberton and others have advocated a low calory diet for this disease but

at the present time medical opinion is turning away from such a point of view There may be occasional instances of overweight patients who need a low calory diet, but these are exceptions to the rule

The use of vitamins in the treatment of arthritis is purely empiric However a good many patients feel better while taking vitamins and therefore their use is recommended

Some such schedule as the following may be advised

Cod liver oil and viosterol one capsule twice a day (vitamins A and D) The highly concentrated preparations of vitamin D (Ertron and others) which have been hailed by some writers as a cure for rheumatoid arthritis have no advantage over the less concentrated preparations

Orange juice and tomato juice one glass of each a day (vitamin C)

Wheat germ or brewer s yeast once or twice a day (vitamin B)

Concentrated vitamins in the form of thiamine chloride and cevitamic acid may be administered hypodermically or by mouth if it seems desirable Some writers prefer to give cod liver oil in the unconcentrated form The chief objection to the unconcentrated product is its tendency to upset the stomach

Vaccine and Protein Therapy —Streptococcus vaccine has been used for years in the treatment of rheumatoid arthritis and is still popular with many physicians Autogenous vaccines however are not used so much now as formerly Both the subcutaneous and intravenous methods of administration have been employed A certain number of patients show benefit by both methods of injection but the intravenous method appears to yield better results

In using streptococcus vaccine, caution must be taken against overdosage When an amount of streptococcus vaccine greater than the patient can tolerate is injected into the vein a sharp exacerbation of joint symptoms often results and in some instances a definite relapse may occur

Foreign protein therapy has been advocated as a method of treating arthritis but is not very popular at the present time Various substances such as milk horse serum peptone and proteoses and typhoid vaccine have been injected intramuscularly or intravenously with the idea of mobilizing the patient's immune bodies or producing a sharp febrile reaction Of the various agents employed typhoid vaccine is the most popular

Fever Therapy —In the writer's opinion fever therapy has a definite though limited place in the treatment of rheumatoid arthritis It is not recommended, however, for the chronic well established cases In the initial stages of the disease particularly in acute febrile cases fever therapy will sometimes bring about a rapid and complete cessation of symptoms Unfortunately a considerable number of these patients who are relieved by fever therapy will suffer a relapse after a few weeks or months of comfort

There are two methods of inducing fever (1) *typhoid vaccine intravenously* (2) artificial hyperthermia by some form of hot box

TYPHOID VACCINE administered intravenously is the simplest and in the author s opinion the safer method of employing fever therapy At the New York Hospital we have used it on many arthritic patients without any untoward effects It has been found particularly helpful in the active febrile type of case The first dose should be 25 000 000 to 50 000 000 with gradual increase in subsequent doses so as to obtain a good chill and febrile reaction with each injection Typhoid vaccine therapy is contraindicated in patients with chronic cardiac disease in elderly patients and in individuals who give a history of tuberculosis

ARTIFICIAL HYPERTHERMIA —In recent years the artificial production of fever in patients by the use of electricity or the hot box has come into vogue for the treatment of various conditions and some writers have advocated its use in the treatment of rheumatoid arthritis Artificial fever is produced by several methods (1) the *hot bath,* (2) high frequency diathermy currents (3) *radiothermy* (4) *electrically* heated cabinets In the writer s opinion hyperthermia by induced heat has more disadvantages than typhoid vaccine The production of heat by radiant energy seems to be the preferable method because of its cheapness simplicity and freedom from danger A number of articles have recently appeared in

which it is pointed out that artificial fever therapy in the treatment of rheumatoid arthritis usually gives only temporary relief This point of view coincides with the author s experience

Drugs—Drugs play a comparatively minor part in the treatment of rheumatoid arthritis The few that are used however are important

Iron in the form of ferrous sulfate 3 grains (0 2 Gm) four times a day, or reduced iron 10 grains (0 6 Gm) three times a day is useful in combating the secondary anemia which is so common with this disease though too often the results are disappointing

Salicylates—For the control of pain there is no drug that stands up as well month after month as acetylsalicylic acid The dose should be 10 grains (0 6 Gm) 3 to 4 times a day and in some patients even larger doses are well tolerated There is less danger of gastric disturbance if the drug is combined with sodium carbonate or taken with food or a glass of milk In severe cases the writer sometimes combines aspirin with aminopyrine and phenacetin in a formula such as the following

Acetylsalicylic acid	gr v	(0.3 Gm)
Aminopyrine	gr iss	(0 1 Gm)
Phenacetin	gr iss	(0 1 Gm)

When the pain is not controlled by these drugs codeine ½ grain (0 03 Gm) may be necessary Codeine seems to work particularly well in combination with aspirin

The analgesic effect of alcohol should not be forgotten A small drink of whiskey or some other alcoholic beverage will do much to brighten the end of the day for the arthritic and usually gives definite relief from pain Many physicians are in the habit of prohibiting alcoholic beverages for patients with arthritis The writer however has rarely seen any ill effects from the moderate use of alcohol

Sulfur therapy has been quite extensively used in clinics but we have never been able to discover any beneficial properties in it Freyberg s careful metabolic studies on the use of sulfur in rheumatoid arthritis would seem to dispose of any theoretical basis for the use of sulfur therapy

Gold Salts—During the last decade various salts of gold have been tried with considerable success in the treatment of rheumatoid arthritis This form of therapy was originally introduced by Forestier, and has received enthusiastic support from various clinics in England and America The mechanism by which gold acts in rheumatoid arthritis is not understood It has been shown however that gold salts possess chemotherapeutic properties against hemolytic streptococci and certain other pathogenic bacteria Sabin and Warren have studied the effect of gold compounds on experimental arthritis in mice which they produced by intravenous injections of pleuropneumonia like organisms Various gold salts were found to exert a definitely curative effect on this disease and the earlier the treatment was begun the more complete and rapid was the therapeutic response Other investigators have shown that gold salts have an inhibitive effect on experimental hemolytic streptococcal arthritis in mice and rats

In recent years some interesting and important studies have appeared on the metabolism of gold when injected into the human body Freyberg and his co workers have studied the rate of absorption and excretion of various gold salts when injected into human subjects These writers found that about 75 per cent of gold is retained in the body during a course of gold therapy while the other 25 per cent is excreted for the most part through the urine and a small part through the feces The gold salt continues to be excreted for weeks even months after the injections have been concluded This slow excretion of gold products probably explains the toxic effects which are sometimes produced

The most popular forms of gold now in use are sodium gold thiosulfate the aurothiomalate of sodium (Myochrysine) and aurothioglucose (Solganal B) The sodium gold thiosulfate is usually administered intravenously while Myochrysine and Solganal B are injected deep into the gluteal muscles The dosage of gold salts has been a matter of considerable controversy In the beginning of gold therapy the dosage varied from 100 to 500 mg It was soon discovered however that such doses were extremely dangerous Freyberg has shown that a dose

of even 100 mg is unnecessarily large and that smaller doses will produce almost equally good clinical results At the present time the doses which are advocated by most authorities in America are as follows

First dose	*10 mg* intramuscularly
Second dose	*25 mg* intramuscularly
Third and succeeding doses	*50 mg* intramuscularly

The interval between doses is one week *Some writers* advise one repetition each of the small doses before proceeding to the maximum dose The total amount administered in the course should be 750 to 1000 mg It is customary to administer gold therapy in several series or courses with intervals of four to eight weeks between The reason for these intervals is to permit the body to excrete some of the accumulated gold The writer and his co workers at the Cornell Arthritis Clinic have now treated over 500 cases of rheumatoid arthritis with gold salts The first 245 cases so treated were recently analyzed with the following results

RESULTS WITH GOLD THERAPY IN 235 CASES OF RHEUMATOID ARTHRITIS

Result	Cases	Per Cent
Remission	62	31
Greatly Improved	68	35
Moderately Improved	39	20
No Improvement	28	14
Total	197	
Insufficient Treatment	38	
Total	235	

* 10 cases of ankylosing spondylitis excluded

Similar results have been reported by Dawson and Boots and other American investigators Gold therapy is now considered by many to be the most satisfactory single agent in the treatment of rheumatoid arthritis It is particularly valuable in early cases that have swelling and pain in the joints but are still free from ankylosis and deformity

Unfortunately gold therapy is attended by certain dangers which militate strongly against its general acceptance Approximately 25 per cent of the patients on gold therapy develop a rash or some other form of gold intoxication such as stomatitis or gastro enteritis Depression of the bone marrow has been observed in a number of cases with a consequent development of hemorrhagic purpura, aplastic anemia or agranulocytosis A few cases of acute nephritis have followed its use and rare instances of toxic hepatitis Because of this tendency toward gold intoxication, which is occasionally fatal patients who are subjected to gold therapy must be watched carefully for reactions A blood count and urinalysis *should be made at least once a month and* the skin carefully watched for drug rashes In spite of careful watching however, an occasional patient will develop an exceedingly unpleasant and persistent exfoliative dermatitis

Another disappointing feature of gold therapy is the comparatively high percentage of relapses, 40 per cent in the author s reported series Because of this tendency to relapse we have recently been giving our patients maintenance doses of gold salts after the regular course of treatment has been completed The maintenance dose consists of 25 mg of gold salt administered intramuscularly every two to three weeks It is too early to draw conclusions as to the value of the maintenance dose but we have obtained the impression that the percentage of relapses is considerably reduced by this procedure

Patients on gold therapy should have determination of the sedimentation rate of the red blood cells about every two to three months Patients who react well to gold therapy usually have a rapid drop in the sedimentation rate during the first course of treatment Furthermore it has been our observation that those who receive marked benefit from gold salts usually show striking improvement from the first course of gold therapy If a patient shows no improvement after two courses of gold therapy further administration of the agent is contraindicated

Sabin has recently introduced a new gold salt quite similar to Myochrysine, but with calcium substituted for sodium (calcium gold thiomalate) This salt is insoluble and is suspended in oil for intramuscular injection When the calcium salt is injected by the intramuscular route the plasma levels are considerably lower than those observed after the injection of comparable amounts of sodium gold thiomalate Furthermore

much less of the gold is excreted in the urine This salt was introduced with the hope that it would prove less toxic than the more soluble forms of gold salts However drug rashes have also been reported following the use of calcium gold thiomalate and in a limited experience at the Cornell Arthritis Clinic the therapeutic results have quite possible to do more harm than good by this method of treatment

Heat is perhaps the most important form of physical therapy and can be applied either locally to the joint or to the entire body The local application of heat to one joint is carried out by means of the ordinary electric baker or by diathermy Some

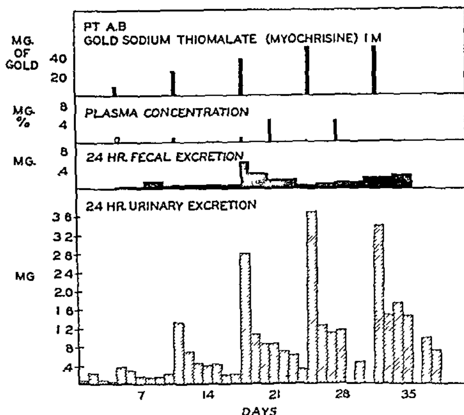


Fig 181—Graphic representation of a typical response in a patient with rheumatoid arthritis treated with increasing doses of gold sodium thiomalate (Myochrysine) injected intramuscularly The plasma gold concentration rises to reach a level of approximately 0 4 mg per cent when 50 mg of gold (100 mg of the drug) are injected Fecal excretion is irregular and increases with larger doses Urinary excretion of gold is always greater on the day of injection it is greater with larger doses Combined excretion however is small compared to the intake of gold and this graph indicates retention of approximately 75 per cent to 80 per cent of the gold injected during the period of treatment This is typical of all cases (Courtesy of Dr Richard H Freyberg)

not seemed so favorable as those achieved with Myochrysine or Solganal B

Physical Therapy—The more common types of physical therapy such as dry heat diathermy massage and exercises all have a place in the treatment of rheumatoid arthritis Their chief function is to increase circulation in the affected joints and to preserve as far as possible the tone of the skeletal muscles Physiotherapy in all forms must be skilfully applied otherwise it is prefer moist heat in the form of hot towels or submersion of the joint in hot water In the experience of the writer diathermy is usually disappointing in the treatment of rheumatoid arthritis From a theoretical standpoint diathermy should be ideal as it heats the tissues as well as the skin but practically a good many rheumatoid patients especially those in the active stage complain that diathermy actually *increases* the pain One of the simplest ways of ap

plying heat to the joint is by means of infra-red light Generalized heat is best applied by means of the hot tub bath the hot pack or the *electric light bridge* The advantage of generalized heat is that in addition to stimulating the circulation copious perspiration is induced in the patient *Hydrotherapy* has come to have an important place in the modern treatment of arthritis The rheumatism cures of Europe date back to the Roman Empire and are still very popular both on the Continent and in Great Britain The European spas which make a specialty of arthritis are Bath and Harrowgate in England Aix les Bains and Dax in France Wiesbaden and Baden Baden in Germany Bad Gastein in Austria and Piestany in Czechoslovakia Alternating hot and cold baths or contrast baths as they are usually called have the advantage of stimulating the sympathetic system as well as the local circulation in the joint

Massage complements heat in that both have more or less the same object—the improvement of blood and lymph flow through the joints Successful results in the use of massage depend on the qualifications of the masseur *and the proper selection of cases* for massage therapy Massage is contraindicated in any patient whose joints are in a highly active painful stage However in many chronic cases there is very little tenderness *on pressure over the joints and in* such cases massage can be used to great advantage not only to the joints themselves but to the adjacent muscles as well Massage is of great value in preventing and correcting the contractures that so frequently occur in rheumatoid patients at the knees and elbows Massage and passive movements preserve the elasticity of the muscles and by increasing the blood supply prevent the gradual shortening of the flexors

Exercises—The object of exercises and calisthenics is first to preserve the function *of the joint by preventing ankylosis,* second to maintain the tone of the muscles and third to prevent and overcome contractions and deformities Every arthritic should have some exercise and one of the most important factors in the treatment of arthritis is to determine just the right balance between rest and exercise in the patient s routine In the average case *with several swollen fingers* or knuckles and a certain amount of swelling and cartilaginous injury in the knees and feet ordinary calisthenics taken lying down will usually serve the purpose The reason *for the recumbent posture is to prevent* strain and fatigue The arthritic is often unable to understand why they are advised to take calisthenics and yet are forbidden to walk or stand The reason of course is that *standing and walking both introduce* a certain amount of strain and friction in the joint whereas when the patient is in the recumbent position all strain on the joint is removed The tendency of the arthritic *joint is to ankylose The tendency* of the arthritic muscle is to undergo atrophy and contraction Both of these tendencies must be overcome by regular exercises The writer instructs every patient with arthritis as to the type of exercise suitable for his particular case The rhythm of the exercise should be slow as rapid movements may induce stiffness on the following day Perhaps the most important of the exercises are those that have to do with maintaining posture In advanced arthritics passive exercises may be necessary or a combination of passive with active exercises

Colonic Irrigations—Certain patients who are suffering from profound intestinal intoxication may need a colonic irrigation once or even twice a week but the great majority *can obtain an equal* amount of benefit from the proper use of laxatives

Transfusions—Transfusions of blood have been advocated by Copeman *Holbrook* and others Holbrook treated seventy patients in this manner, and found that in the subacute or early phases of infectious arthritis with or without anemia they responded well and *in a few instances dramatically* Transfusions were of little or no help for chronic afebrile patients with advanced bony changes Transfusions are *particularly* valuable in patients who show secondary anemia 500 cc of blood is the amount usually given and it may be repeated a few days later if desirable The indirect method is *quite satisfactory and* simplifies the procedure considerably

Climatotherapy—Some rheumatoid patients respond well to a change *of* climate, particularly when they are transferred to a dry warm climate such as that of Arizona

or New Mexico Holbrook believes that the various forms of heliotherapy constitute the major portion of specific climatotherapy A physician who advises a patient to go to Arizona should stress the importance of his remaining there for at least six months or even a year Patients who for financial or other reasons cannot make the pilgrimage to the Southwest should be exposed as much as possible to sunlight and dry heat at home

Orthopedic Treatment—If every case of rheumatoid arthritis could receive prompt and efficient medical treatment comparatively few of them would need orthopedic measures Unfortunately there are a good many individuals who for one reason or another do not receive prompt medical treatment or perhaps they are lacking in resistance to the disease and advance rapidly to ankylosis and deformity For such patients orthopedic procedures of various kinds are of tremendous importance for both prophylaxis and treatment Some of these measures can be applied to ambulant cases Others can be used only in institutions The amount of rehabilitation which may be achieved even in an advanced case of rheumatoid arthritis is remarkable but such improvement requires months or even years of patient care and supervision

Surgical Treatment—Great strides have been made in recent years in the surgical treatment of advanced arthritic conditions Manipulation under an anesthetic synovectomy osteotomy arthrodesis and various reconstruction and arthroplastic operations all have an important place in modern orthopedic surgery Synovectomy is particularly useful in the correction of rheumatoid knees or elbows which have developed villous arthritis This operation involves the removal almost *en masse* of the proliferative synovial membrane A new synovial membrane may be expected to reform and a good but not complete range of motion is to be anticipated

Sympathectomy of the cervical or lumbar ganglia has been tried but rarely gives permanent benefit It has been found that this method is unavailing even temporarily unless an extreme constricting spasm of the blood vessels exists Such spasm can be demonstrated in only a comparatively few cases of rheumatoid arthritis

Psychotherapy—Most patients with rheumatoid arthritis suffer a great deal from mental depression and consequently need an abundant measure of psychotherapy On the other hand there are some individuals usually men who do not take their affliction seriously enough and the physician in all fairness to the patient should make clear to him the serious potentialities of the disease The small slender type of neurotic woman is particularly susceptible to rheumatoid arthritis and often responds poorly to treatment It is this type of patient that needs the greatest amount of moral encouragement Unless the physician makes very earnest efforts along this line, he will fail to get the full cooperation and confidence of the patient factors that mean much in the stubborn fight against the disease

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DEGENERATIVE JOINT DISEASE

(*Osteo arthritis Hypertrophic or Degenerative Arthritis*)

Definition —Degenerative joint disease *or osteo arthritis as it is usually called* is a chronic arthropathy occurring usually in elderly people and characterized by hypertrophic and degenerative changes in the bone and cartilage In some cases there is considerable thickening of the synovial membrane

Degenerative arthritis occurs in both a generalized and localized form The generalized form is polyarticular and affects both the large and small joints It is a senescent process *occurring in middle aged and elderly* people and its etiology is unknown

The localized form occurs in one or several joints and may be secondary to trauma structural abnormalities or previous infection in the joint It occurs most frequently in the hips knees or lumbar spine

Morbid Anatomy —One of the first changes seen is a slight roughening and dulling of the *cartilaginous surfaces* At the edges of the surface there is more or less *lipping* and spur formation the latter consisting of spongy bone covered with cartilage As these irregularities become more prominent the cartilage is worn away and the underlying bone is finally laid bare The exposed bone becomes dense and hard and takes on a highly polished eburnated surface

Stockman points out that the characteristic change in this disease is a combination of *simultaneous bone absorption and bone production* These changes take place very gradually and irregularly and in *some cases* may lead to considerable bony deformity Chronic bony changes are seen most frequently in the hip, knee spine and finger joints Ossification may occur in the fibrous tissue about the joints and even in the ligaments the tendon insertions and the bursae The synovial membrane in the beginning is altered very little or not at all but later *on it may show thickening and hypertrophy* of the villous processes These changes in the *synovial membrane apparently* are due to trauma from the bony deformities to which they are secondary Small cartilaginous tumors sometimes form in these hypertrophied villi and when they become free in the joint cavity constitute the so-called joint mice The synovial fluid may or may not be increased in amount

In this form of arthritis the joint cavity *is never obliterated The joint may be* partially dislocated but the synovial membrane does not form adhesions and ankylosis does not occur A certain amount of locking may be present due to a new growth of bone about the edges of the joint

Etiology —Degenerative arthritis is sometimes called senescent arthritis as it occurs almost exclusively in middle aged and elderly people *It is particularly common* in women at the time of menopause As the *years advance* the wearing quality of the joint is diminished depending possibly upon some disturbance in the local circulation Just as the teeth wear down in many old people so the joints particularly the weight bearing joints are prone to wear out in the middle aged and elderly

It is generally agreed that degenerative arthritis has no specific etiology It is more *prevalent in some families* than in others so no doubt heredity is a factor

Perhaps the most important single etiologic factor is trauma The trauma may be in the nature of a mild and long-continued irritation or an acute *rather violent* form, such as might result from an accident or *fracture The trauma* to the weight bearing joints which results from overweight is one of the most frequent causes of degenerative

arthritis In such cases the knees hips and lumbar spine are the joints which suffer most

Physical defects such as curvature of the spine abnormalities of the vertebrae and flat feet predispose to hypertrophic changes in the pine of middle aged patients

Faulty posture predisposes to hyper trophic arthritis by putting an unnatural strain on the joint, or by bringing about unequal pressure on the joint surfaces In correct sitting or standing places a strain on the lower spine, and an improper gait puts an unnatural tension on the joints of the leg particularly on the knee and ankle joints Obese patients nearly all have a bad posture The lower abdomen is abnormally prominent the upper back is rounded and the shoulders pushed forward The feet are abducted producing a distinct tendency to ward knock knee This posture leads to a strain on the lumbar spine as well as on the knees and feet a condition which of course is accentuated by the overweight of the pa tient.

Occupation has an important bearing on the etiology of degenerative arthritis La borers and mechanics are affected most often Any joint which is subjected to con stant usage is apt to show symptoms in an elderly patient

Exposure is possibly a predisposing factor in degenerative arthritis though certainly to a less extent than in rheumatoid arthritis Elderly people who lead hard and exposed lives appear to be more prone to degenerative arthritis than those whose circumstances are more fortunate Persons who keep their hands in water a large part of the day are subject to degenerative arthritis in late life

Symptoms and Physical Signs—The onset of hypertrophic arthritis is insidious The patient usually middle-aged or elderly first notices a slight stiffness in the affected joint which gradually becomes more un comfortable especially during exercise The disease progresses more slowly than rheu matoid arthritis As time goes on however the symptoms become more marked and there may be constant pain in the joints involved The joints most frequently af fected are the hips knees fingers and verte-brae although under certain conditions any joint in the body may undergo hypertrophic changes

On physical examination the patient is usually middle-aged and overweight and the weight bearing joints are the ones generally affected The posture is often bad and there is usually some degree of flatfoot The af fected joints are rarely swollen and never ankylosed On movement some crepitation is usually noted Occasionally there may be an increase of fluid in the joint cavity When the affected joint is palpated it may be pos sible if the joint is superficial to feel the hypertrophied bony outgrowths around the margins of the joint

Diagnosis—The diagnosis of primary osteo arthritis can usually be made without much difficulty The age of the patient and the gradual onset of pain and stiffness in one or more joints without soft tissue swell ing are almost sufficient evidence on which to make a presumptive diagnosis The pres ence of crepitation in the joint gives addi tional support and the finding of the char acteristic bony changes in the x ray con firm the diagnosis The sedimentation rate should be normal or only slightly elevated If symptoms are limited to one joint the history of trauma should make one very suspicious of an osteo arthritis even before x rays have been examined An experienced internist will always suspect an osteo arthritis of the knees when an obese middle-aged woman limps into the consultation room[7]

Some confusion may arise in those cases which are often labeled mixed arthritis where osteo arthritis is superimposed on a preceding rheumatoid or infectious arthritis It is a fact that the two great types of chronic arthritis the rheumatoid and the degenerative can exist in the same joint one form being superimposed on the other It is also important to remember that a mild osteo arthritis can exist in a joint without causing symptoms and that in many cases of osteo arthritis of the lumbar spine the pain is due not so much to the osteo arthri tis as to bad posture developmental abnor malities spinal curvature and so on

Laboratory Findings—The sedimentation rate of the red blood cells is normal or only slightly accelerated The patient s serum re-veals no streptococcal agglutinins The blood

sugar may be elevated The basal metabolism is often below normal

X ray Examination—In hypertrophic arthritis characteristic findings can be made out in the radiographs fairly early in the disease In incipient cases these changes take the form of bony lipping and spur formation along the articular margins of the bone In the later stages the joint interval is narrowed and there is erosion of the articular bone and alteration in the shape of the articulating surfaces The surface itself however remains well defined and there is some condensation of bone immediately below the articular surface The periarticular lipping becomes more marked as the disease progresses

The *differential diagnosis* of osteo arthritis from rheumatoid arthritis has been discussed in the section on rheumatoid arthritis Osteo arthritis is occasionally confused with gout though such should rarely happen The clinical course of gout is very characteristic with its paroxysmal and intermittent attacks the presence of tophi and an elevated uric acid level in the blood should serve to identify it Secondary osteo arthritis is frequently seen in patients with chronic tophaceous gout Osteo arthritis should never be confused with a Charcot joint which develops suddenly with a large effusion and is free from pain tenderness and heat The x ray findings are quite different in the two conditions and positive Wassermann and spinal fluid reactions should identify the Charcot joint

Prognosis—There is no cure for an osteo arthritic joint that is to say the destruction of cartilage and the hypertrophic changes in the bone are permanent However the progress in osteo arthritis is usually very slow and the prognosis is much better than in rheumatoid arthritis In many cases the patient s discomfort can be completely relieved by proper treatment even though the pathologic changes in the joint persist This is particularly true in the case of the knees and back where weight reduction physiotherapy and orthopedic measures often give marked relief

Special Forms—Hypertrophic arthritis occurs in a number of well recognized clinical forms

Morbus Coxae Senilis—This form of osteo arthritis occurs in the hip It usually develops in middle age, in patients well past fifty, though occasionally it is encountered in the forties

Etiology—Osteo arthritis of the hip is nearly always referable to trauma in the form of either an actual injury or repeated small injuries such as might result from constant overuse of a joint The condition as the title indicates is usually monarticular though occasionally one sees both hips affected

Symptoms—The patient is middle-aged or elderly In the early stages the patient with osteo arthritis of the hip complains of pain in the distribution of the sciatic, obturator or anterior crural nerve At this stage it may be mistaken for neuritis In the later stages the pain is related more definitely to the hip joint and also to the knee joint indeed in some cases the symptoms in the knee joint are so pronounced that the physician is led to a mistaken diagnosis of disease in the knee joint, while the affected hip joint entirely escapes attention

The patient walks with a limp with his weight on the unaffected side On palpation of the joint in a well developed case crepitation is readily made out On passive movement of the hip joint rotation abduction and other movements may be much limited

Diagnosis—The diagnosis of degenerative monarticular arthritis usually can be made without much trouble from the symptoms and physical signs A middle aged or elderly man complains of increasing pain and stiffness in one hip He probably gives a history of a fall or some other trauma affecting the hip joint If on examination crepitation is made out the presumptive diagnosis is morbus coxae senilis As in other forms of degenerative arthritis the final diagnosis is made by x ray Radiographs disclose the characteristic lipping and spur formation with thinning of the joint space. Later on degenerative changes occur in the bone In long standing cases there may be some deformity resulting from absorption of the head and shortening of the neck of the femur

Heberden s Nodes—One of the mildest and commonest forms of osteo arthritis is the so-called Heberden s node These

nodes begin to make their appearance in middle life, particularly in the female sex and manifest themselves as bony outgrowths around the bases of the terminal phalanges They are more prone to develop in people who work hard with their hands

SYMPTOMS —The development of Heberden s nodes like that of other forms of osteo arthritis is slow and insidious and causes little inconvenience usually it does not even interfere with the normal movements of the joints Many times they are free from tenderness and pain Sometimes however particularly in the early stages they may occasion a good deal of pain and some limitation of movement At times the nodes undergo exacerbations and become a little more swollen and tender than usual The lesion may appear on only one finger but as a rule several or all of the distal phalangeal joints are involved

Menopausal Arthritis or Arthrosis —This type of arthritis occurs in two forms (1) in women who have been subject to artificial menopause by hysterectomy or deep x ray therapy In such patients the disease may appear even in the early thirties (2) cases developing during or immediately after normal menopause The age of onset in these cases is usually between forty five and fifty five

In most cases the symptoms of discomfort are most noticeable in the knees fingers and lumbar spine and x ray examination will show the usual hypertrophic changes in the bones Many students object to the term menopausal arthritis' and believe that all of these cases should be classified as degenerative arthritis However there are some cases particularly those seen in younger women in which careful examination reveals no signs of osteo arthritis For such cases the term menopausal arthrosis has been suggested

Symptoms develop insidiously the first signs of discomfort usually being in the knees A large percentage of these patients show Heberden s nodes on the distal phalangeal joints The progress of the disease is very slow and there is little tendency toward involvement of other joints

Hypertrophic Spondylitis —The vertebrae of most people past fifty years of age will show some evidence of this condition The bodies of the vertebrae undergo more or less hypertrophy and lipping at their bases and there may be some ossification of the ligaments The articular processes of the vertebrae may be enlarged eburnated and marked by bony outgrowths Actual ankylosis does not occur but there may be considerable limitation of movement due to the marked bony changes

This condition develops very slowly, usually without much pain The bony outgrowths may press on nerves however, and



Fig 182—Radiograph of the knee joint of an elderly woman showing degenerative arthritis Note thinning of the cartilage over the inner condyle and bony lipping around margins of joint (From Oxford Monograph Cecil s Diagnosis and Treatment of Arthritis courtesy of the Editor Dr Henry A Christian and Oxford University Press)

produce pain and paresthesias Other joints may show bony changes particularly the hips and knees

Treatment of Hypertrophic Arthritis —The successful treatment of osteo arthritis depends upon a correct evaluation of the etiologic factors Perhaps the most important feature of the treatment is rest for the affected joints In obese patients weight reduction is best accomplished by a low calory diet supplemented by thyroid extract for those patients whose basal metabolism is below normal Sodium iodide intravenously once or twice a week has been recommended

for this type of arthritis If oral treatment is desired, hydriodic acid, 1 drachm (4 cc) three times a day in a half glass of water can be employed Physiotherapy and other forms of heat give much relief, but care must be taken in massaging affected joints lest trauma be induced over the hypertrophied margins of bone Deep x ray therapy has been recommended by some writers but in the author's experience is rarely effective

Treatment of Special Forms—The treatment of osteo arthritis of the HIP is difficult and unsatisfactory As long as the pain is not too severe rest and other conservative measures are all that should be attempted When the pain and disability are severe surgery may become necessary In such cases, arthrodesis gives complete relief but leaves the patient with a stiff hip joint Plastic operations particularly the vitallium cup operation, are quite popular with some surgeons

Painful HEBERDEN'S NODES are often relieved by resting the hand as much as possible and by the local use of heat In this connection the paraffin bath is often helpful The method of applying paraffin is as follows

Equipment—A candy or fat thermometer
2–4 pounds parawax
1 piece of oil silk 12" x 14
1 square absorbent cotton and piece of wool

Melt parawax over slow fire then remove from stove and allow it to cool until the thermometer registers 110 to 120 F Having soaked the hand for about three minutes in hot water and while still wet dip in and out of the parawax twelve to fifteen times Quickly wrap oil silk about parawax which has accumulated on hand then around that the cotton and a piece of wool about the whole so that the heat may be retained Let hand rest quietly in the paraffin pack for about an hour Then remove the wax which may be used for the next application

MENOPAUSAL ARTHRALGIA when unaccompanied by osteo arthritic changes is often greatly relieved by estrogenic therapy, 2 000 to 10 000 rat units twice a week administered every three to five days As the patient improves oral treatment can be substituted for the parenteral injections Stilbestrol 0 5 to 1 0 mg in tablet form sometimes gives very good results It is much cheaper than the natural hormone but is more likely to cause gastro intestinal symptoms When menopausal arthralgia is accompanied by osteo arthritis, the therapeutic measures described above should be instituted in addition to the hormone therapy

The treatment of hypertrophic spondylitis should be that of osteo arthritis in general but if the discomfort persists in spite of physiotherapy and other symptomatic remedies orthopedic measures may be necessary Many of these patients become dependent on a strong back brace for the relief of pain

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ARTHRITIS ASSOCIATED WITH DISTURBANCES OF METABOLISM

The arthritic manifestations associated with gout and other diseases of metabolism are discussed in the sections which deal with these diseases

ARTHRITIS OF NEUROPATHIC ORIGIN

The joint manifestations of tabes syringomyelia and peripheral nerve lesions are discussed in the sections which deal with these diseases

NEOPLASMS OF THE JOINTS

Benign or malignant new growths involving any of the structures of a joint produce symptoms which may simulate arthritis

Benign soft tissue tumors, such as lipoma hemangioma or cystic degeneration of the external semilunar cartilage of the knee excite mechanical disorders such as limitation of motion locking and synovial effusion Single or multiple xanthomata arising in the synovium (usually in the knee) produce symptoms similar to any low grade synovitis The synovial fluid which is often yellowish brown is sterile The blood cholesterol is usually elevated Synovioma is a similar but definitely malignant tumor

Bone tumors occurring near joints such as giant-cell tumors, multiple or single bone cysts osteogenetic sarcoma and metastatic carcinoma cause stiffness, swelling pain limitation of motion and even deformity if destruction of bone has been sufficient to produce a pathologic fracture

Although the disability may be great, there is usually very little local heat or redness With malignant tumors the general condition of the patient rapidly deteriorates

The treatment of joint neoplasms is surgical and orthopedic

RUSSELL L CECIL

MECHANICAL DERANGEMENTS OF JOINTS

Traumatic Arthritis —Any injury to the cartilage bone or ligaments of a joint is apt to produce persistent or transient pain swelling and limitation of motion When the joint is badly sprained temporary effusion of fluid may take place in the joint cavity Traumatic arthritis is often an important predisposing factor in the development of a localized osteo arthritis

The *treatment* of traumatic arthritis consists of rest physiotherapy and orthopedic measures if necessary

Joint Disturbances Secondary to Abnormal Postural Strain —Pronation of the feet poor posture and congenital or acquired deformities produce undue strain on the weight bearing joints and if not corrected may in the course of time lead to the development of secondary osteo arthritis Deformities such as congenitally flat feet knock knees and spinal scoliosis are particularly important predisposing factors Obesity is another common cause of joint disturbance secondary to postural strain

The *treatment* consists of correction of the postural strain

RUSSELL L CECIL

MISCELLANEOUS FORMS OF ARTHRITIS

Arthritis of Serum Sickness —This form of arthritis is described in detail in the section on serum sickness page 486

Arthritis of Hemophilia —The arthritis of hemophilia is discussed in the section on hemophilia page 984

Intermittent Hydrarthrosis —This is a rare and peculiar condition of the joints characterized by acute regularly recurring effusions of fluid into the joint cavity The etiology of this disease is still obscure There is some evidence to support the theory that it is of an infectious nature but from recent studies it appears more than likely that the disease is an allergic manifestation Schlesinger has pointed out the similarity between intermittent hydrarthrosis and angioneurotic edema Feré and Garrod have each reported a case of intermittent hydrarthrosis in which the disease was associated with generalized urticaria and Burchard refers to a case where hydrops occurred in an asthmatic

The striking features of intermittent hydrops are its periodic recurrence and its tendency to affect the knee joint The exact regularity of the recurrences is the most interesting feature the usual interval being ten or eleven days Sometimes the interval of exact periodicity changes as in one of the reported cases where the interval after having been twelve days changed to six When several joints are involved the swelling may appear in all simultaneously or in one earlier than in the others The average duration of each attack is from four to five days During the attack the joint is distended with fluid and the patient is rarely able to use the extremity because of the resulting pain In the interval between attacks the joint in most cases is practically normal although in some patients there may be a residual stiffness between the acute attacks A slight rise in temperature and a leukocytosis have been reported in some cases According to Miller and Lewin one or both knees have been involved in every case reported in the literature Occasionally additional joints are

implicated, such as the wrist or hip, and some cases progress into typical rheumatoid arthritis

The *diagnosis* is comparatively easy and is based on the following criteria

1 Acute attacks of effusion of fluid into the joint (usually a knee) occur at regular intervals of ten to eleven days

2 After a period of four to five days, fluid disappears from the joint almost as rapidly as it forms leaving the joint practically normal

3 Puncture of the joint reveals clear and practically normal joint fluid

The *treatment* of intermittent hydrops is rather unsatisfactory Fortunately a certain number of cases recover spontaneously During the acute attack the patient should rest in bed or in an easy chair Local discomfort may be relieved by hot applications and acetylsalicylic acid three times a day Miller and Lusk obtained excellent results by intravenous injections of typhoid vaccine but in the writer s experience the relief obtained has been only temporary Krida has reported complete and permanent cure by synovectomy, and favorable results have been obtained by others

Pulmonary Osteoarthropathy —The arthritic manifestations of pulmonary osteoarthropathy are discussed in the section on this disease p 1322

Hysterical Joints —Joint symptoms can occur without any organic basis Partial or complete fixation of a knee in full extension or a foot in equinus varus may be a purely hysterical phenomenon Other patients especially compensation cases may present many of the features of arthritis of the spine or those of an internal derangement of the knee Subjective complaints overshadow physical findings Swelling and local heat are absent Tenderness is often too acute to be genuine Typically hysterical conditions such as paralysis or paresthesias may occur in the same patient

The *treatment* is that for hysteria

Other Joint Disturbances —There are various other disturbances which are not classifiable as arthritis but which cause more or less pain in the affected joints Among such should be mentioned aseptic necrosis of the bone, loose bodies in the joint osteochondritis dissecans osteochondromatosis, and others For discussion of these topics the reader is referred to any standard textbook of orthopedics

Russell L Cecil.

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DISEASES OF THE BONES

OSTEOMALACIA

Definition —Osteomalacia is a calcium phosphorus deficiency disease characterized by distinct metabolic and histologic changes which are readily restored to normal if adequate therapy is administered Histologists are agreed that in rickets and osteomalacia the essential abnormality is the same namely, a deficient calcification of all osteoid tissue The term, osteomalacia should never be employed to designate any of the other skeletal diseases characterized by generalized decalcification

Incidence.—Osteomalacia is endemic over wide areas in northern India, northern China and Japan and sporadically in certain parts of Europe. It is rare in the United States of America, most of the cases being associated with chronic steatorrhea It is primarily a disease of women and is apt to occur earlier and with greater severity in each succeeding pregnancy The *hunger osteopathy* observed in Germany and in Poland between 1917 and 1919 probably represented varying grades of osteomalacia The histologic findings and the response to vitamin D therapy support this interpretation

Etiology —Before it was known that osteomalacia was a deficiency disease various etiologic theories were proposed Hyperactivity of the ovaries, leading to hyperemia of the bones and a resulting decalcification was long accepted as a cause of osteomalacia. This theory was not based on accurate

experiment nor was there any evidence that the ovaries were abnormal Nevertheless oophorectomy was for a time the routine treatment for osteomalacia The treatment of osteomalacia with adrenalin likewise was based on fallacious reasoning Today it is agreed that osteomalacia and rickets are the same disease Osteomalacia is frequently referred to as *adult rickets* Resorption and formation of bone continue but calcification of the newly formed osteoid tissue fails to take place because of insufficient absorption of calcium and phosphorus from the gastro intestinal tract. The impaired absorption may be due to (1) privation (2) marked alterations of the calcium to phosphorus dietary ratio (3) increased intestinal rate, (4) decreased acidity of the gastro intestinal tract (5) steatorrhea and (6) vitamin D deficiency Rarely is the disease due to one cause Vitamin D deficiency is operative in all cases Privation alone does not cause the disease In this country most cases are associated with chronic steatorrhea As a result of the faulty digestion and absorption of fats insoluble calcium soaps are formed and the fat soluble vitamin D is excreted in the excess fat. That vitamin D lack is the chief cause of the calcium phosphorus deficiency is well demonstrated by the dramatic clinical and metabolic improvement which follows its administration in adequate amounts The osteomalacia of northern China and India is the result of a diet deficient in calcium phosphorus and vitamin D isolation from the sun because of environment and customs and the calcium drain of oft repeated pregnancies and long continued lactation That this type of osteomalacia is due chiefly to a lack of vitamin D was adequately demonstrated by Maxwell who noted both clinical and metabolic improvement when cod liver oil was given even though the dietary remained inadequate in respect to calcium and phosphorus

In normal individuals a minimal amount of calcium and phosphorus is excreted daily irrespective of the intake of such salts In the states of pregnancy and lactation the loss of calcium and phosphorus is further increased In osteomalacia because of deficient absorption the entrance of these salts into the body is less than the loss there from and in consequence a negative calcium and phosphorus balance results. Metabolic studies reveal an increased excretion of calcium and phosphorus in the feces and decreased urinary excretions This failure to absorb sufficient calcium and phosphorus results in a deficiency of these salts in the body fluids and an inadequate deposition of calcium and phosphorus in the newly formed osteoid tissue In severe osteomalacia a negative calcium and phosphorus balance may persist despite a high intake of calcium and phosphorus In such instances the serum calcium and phosphorus are decreased and the serum phosphatase elevated In the milder cases the serum calcium may be normal or only slightly reduced the serum phosphorus lowered and the serum phosphatase only slightly increased

Morbid Anatomy—The gross skeletal deformities encountered in osteomalacia vary with the severity of the disease and its duration and are not present in the milder cases. In the severe types the pelvis thorax spine and long bones may be deformed in a haphazard manner In such cases a severe kyphoscoliosis may reduce the height by several inches and cause the head and neck to sink downward and forward upon the chest The bones are soft and flexible rather than fragile so that bending is more common than spontaneous fractures although both may occur The bony cortex is thin and often shell like the trabeculae are greatly reduced in number or absent and the marrow spaces are enlarged

Microscopically the striking feature is the deficient calcification as shown by the wide osteoid seams Normal physiologic resorption continues Osteoclasts are normal in number but osteoblasts are very abundant The wide osteoid seams the numerous osteoblasts the absence of considerable fibrous tissue and the infrequency of osteoclasts should serve to distinguish osteomalacia from hyperparathyroidism or osteitis deformans

Symptoms—The symptoms of osteomalacia are directly proportional to the severity of the disease In the mild form the patients may complain only of weakness pains in the bones of the legs or the lower part of the back on standing and walking A patient with severe osteomalacia may seek medical

and because of the distressing *symptoms* of severe tetany (see p 1247) Another patient may suffer from a crushed vertebra *from* moderate *lifting* or a minor fall In the advanced *cases* severe backache is a common symptom The bone pain is aching in character oftentimes generalized and worse in the winter when lack of vitamin D is greatest Muscular weakness is often marked, a waddling gait is not uncommon and the bones are often sensitive to light pressure The skeletal deformities previously mentioned may be present

Roentgenologically one finds generalized decalcification thinning of the cortices bowing, fractures and deformities of the type mentioned

Diagnosis—Tetany occurring in association with chronic diarrhea should always suggest osteomalacia Any skeletal disease characterized by generalized decalcification may be mistaken for osteomalacia the osteoporotic form of hyperparathyroidism senile, idiopathic or postmenopausal osteoporosis the osteoporosis of hyperthyroidism, Cushing's disease, occasionally multiple myeloma metastatic malignant lesions rheumatoid arthritis of the spine and the osteoporosis of disuse

Osteoporotic Form of Hyperparathyroidism—This form of hyperparathyroidism may be indistinguishable from osteomalacia except by means of chemical or pathologic examination. A high serum calcium a low serum phosphorus and an elevated serum phosphatase are diagnostic of hyperparathyroidism If the disease is complicated by the presence of one of the other forms of osteoporosis the osseous changes will be out of proportion to the degree and the duration of the hyperparathyroidism and the phosphatase level will be unexpectedly low for the degree of decalcification In the occasional case of this latter type metabolic studies and histologic examination of a bone biopsy specimen may be indicated

Senile Idiopathic and Postmenopausal Osteoporosis—The diagnosis of this type of osteoporosis is discussed under the section entitled Senile Osteoporosis

Osteoporosis of Hyperthyroidism—An increased excretion of calcium and phosphorus far in excess of that resulting from acidosis or hyperparathyroidism has been observed in severe hyperthyroidism These increased excretions are via the gastro intestinal tract as well as the kidneys If the thyrotoxicosis persists for a period of years the continued loss of calcium and phosphorus will result in generalized osteoporosis Such bone resorption is generalized and homogeneous and results from widespread lacunar resorption The serum calcium, phosphorus and phosphatase are usually normal although the latter may occasionally be slightly elevated There is no relationship between the duration of the disease, the degree of osteoporosis and the slight elevation of the serum phosphatase.

Cushing's Disease (Basophilic Adenoma of the Pituitary and Adrenocortical Syndromes)—This affliction is characterized by osteoporosis most marked in the spine It has many of the clinical characteristics of postmenopausal osteoporosis In Cushing's disease, however, there is a decrease or an absence of the formation of estrogen and in addition an increase in urinary androgens The serum calcium, phosphorus and phosphatase values are normal The associated obesity hirsutism atrophy of the skin and hair purplish atrophic striae amenorrhea and hypertension should serve to differentiate it from osteomalacia

Multiple Myeloma—Rarely is the decalcification of multiple myeloma generalized or homogeneous Decalcification of the spine when present may give rise to ballooned intervertebral disks and collapsed vertebrae Usually, however localized evidence of destruction of bone is seen in the ribs the pelvis and most clearly of all in the skull The pain is more severe than that observed in osteomalacia and persists when the patient is in the recumbent position Hypercalcemia and hyperphosphatemia are often present The serum phosphatase is usually normal These features of the disease the hyperproteinemia and Bence Jones proteinuria should serve to avoid confusion with osteomalacia

Metastatic Malignant Lesions—An osteoclastic type of metastatic malignant lesion may give rise to an extensive osteoporosis of the spine The diagnosis is readily made roentgenologically by the presence of localized areas of destruction invasion of the

pedicles of the vertebrae or regions of destruction in the flat bones

Rheumatoid Arthritis of the Spine—Extensive spinal osteoporosis is frequently seen in individuals suffering from rheumatoid arthritis of the spine In addition to the osteoporosis there is evidence of destructive changes in the sacro iliac joints and the intervertebral facets Calcification of the spinal ligaments may or may not be present These roentgenologic lesions plus the characteristic history and physical findings should serve to differentiate this disease from osteomalacia

Osteoporosis of Disuse—Generalized osteoporosis may be encountered in bed ridden patients whose activities have been markedly restricted by ankylosing arthritis infantile paralysis or prolonged immobilization from other causes. In such cases the stresses and strains of normal activity responsible for normal osteoblastic activity are greatly reduced The ensuing decreased osteoblastic activity results in a decreased formation of osseous matrix and in consequence failure of calcium deposition and osteoporosis Associated with this form of osteoporosis one finds, except in very exceptional instances a normal serum calcium phosphorus and phosphatase However hypercalcinuria may occur in the early stages of immobilization and may lead to renal complications and the formation of urinary calculi In these cases the cause of the decalcification should be obvious

Prognosis.—Osteomalacia responds to adequate therapy The time required for correcting the existing abnormalities depends upon the duration of the disease and its severity

Treatment—The clinical and metabolic response to treatment is usually very prompt and often dramatic This is accomplished by administering a high calcium high phosphorus diet and adequate amounts of vitamin D Such a diet should contain liberal amounts of milk cheese nuts and eggs If the patient s dietary whims prevent such a diet the administration of 3 to 6 drachms (11 6–23.2 Gm) of calcium glycerophosphate will provide a sufficiently high calcium and phosphorus intake The daily administration of 10 000 to 50 000 units of vitamin D in the form of cod liver oil or one of the potent vitamin D preparations will usually suffice Occasionally, the administration of large amounts of cod liver oil has been ineffectual In such instances excellent results are obtained when large amounts of a potent vitamin D concentrate are administered.

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HEREDITARY DEFORMING CHONDRODYSPLASIA

(Multiple Cartilaginous Exostoses Dyschondroplasia Diaphyseal Aclasis)

Definition.—Hereditary deforming chondrodysplasia is a developmental disorder of growth the chief features of which are multiple exostoses and irregularities in growth of the epiphyses The arrested development in the affected bone leads to secondary deformity

Incidence—The disease is frequently encountered Ehrenfried having collected 600 published cases by 1916 Males are more frequently affected than females The disease is often hereditary transmission taking place through the male

Etiology—The exostoses are thought to be due to a proliferation of cartilage cells arising from the epiphyseal plate This proliferation is unchecked by the periosteal sleeve and consequently the calcifying cartilage at the tip of the disk projects outward from the shaft The disease affects only those bones arising from cartilage the membranous bones being exempt

Morbid Anatomy—The exostoses usually appear on the diaphyses of long bones near the epiphyseal lines at the site of muscle insertions The outgrowth of compact bone is continuous with that of the diaphysis This merges into a mass of compact bone the surface of which is covered by cartilage which in turn is enveloped by a connective tissue membrane The exostoses are extremely irregular in shape vary greatly in size, and may be exceedingly numerous

Microscopic examination of an exostosis reveals normal hyaline cartilage the deeper layers of which are undergoing ossification The adjoining cancellous bone usually contains fatty bone marrow The base of the exostosis consists of compact bone similar to that of the cortical bone from which it arises True enchondromata are sometimes seen In addition to the exostoses changes in the shafts of the long bones or in their epiphyses may or may not be present Such deformities occur more commonly in the femur, tibia fibula ulna, and radius The ends of the bones may be wider than normal the cancellous bone rarefied and the interstices filled with myxomatous tissue The retarded and irregular growth of the epiphyses may be the cause of mild to moderate dwarfism and deformities, especially of the genu valgum and genu varum types

Symptoms—While the objective signs are striking primary symptoms are lacking because the exostoses are painless unless they are in an area where they are apt to be injured either by normal use or accident Joint symptoms may arise in consequence of articular distortions and mechanical limitations The development of malignant osteochondromata fracture erosion of a blood vessel with resulting aneurysm pressure on nerve trunks with resulting neuralgia neuritis and paralysis and signs of cord compression have been reported The exostoses appear in childhood but grow most rapidly during the adolescent period when new exostoses may appear

The roentgenographic appearance is quite characteristic Bone deformities such as described above are seen Their density and structure are extremely varied The shaft of the affected bone more often shows decreased density with a longitudinal pencilling of areas of increased rarefaction

Prognosis—The general health is unimpaired and the rare complications seldom affect the length of life Growth of the exostoses eventually ceases and the deformities become fixed at the time of skeletal maturity

Diagnosis—Apart from the superficial resemblance to mild cases of achondroplasia a typical case can hardly be confused with any other disease

Treatment—When the tumors cause unsightly deformities pressure symptoms, or suggest malignancy, they should be removed Excision of the tumor with complete removal of the base will prevent its recurrence

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OSTEITIS FIBROSA CYSTICA

(*Hyperparathyroidism von Recklinghausen's Disease*)

Osteitis fibrosa cystica (generalisata) has been definitely proved to the result of over function of the parathyroid glands A description of this disease will be found in the section on Diseases of the Parathyroid Glands under the title of Hyperparathyroidism p 1250

Walter Bauer

HYPERTROPHIC PULMONARY OSTEO ARTHROPATHY

(*Secondary Hypertrophic Osteo Arthropathy Bamberger Marie's Disease Hippocratic or Clubbed Fingers Osteo Arthropathie Hypertrophiante Pneumique Acropachy*)

Definition—In the disease hypertrophic pulmonary osteo arthropathy there occurs general and symmetric clubbing of the fingers and toes often associated with hyper

trophy of the long bones of the hands and feet and less frequently with painful en largement of the long bones of the forearms and legs These changes are associated with a variety of diseases especially chronic af fections of the lungs and heart Because of this association with diseases of the lungs and mediastinum, it seems appropriate to retain the term hypertrophic pulmonary osteo arthropathy

Incidence —The disease is probably al ways *secondary, although a few cases have* been reported without evidence of ante cedent or associated disease. Of the one hun dred and forty four cases reported by Locke one hundred and twelve were associated with pulmonary disease six disease of the circu latory system thirteen disease of the gas tro intestinal tract and thirteen unknown or miscellaneous diseases The majority oc curred with *bronchiectasis pulmonary tu* berculosis empyema lung abscess malig nant disease of the lung and mediastinum emphysema valvular and congenital heart diseases subacute bacterial endocarditis biliary cirrhosis congenital syphilis and chronic enteritis No age group is exempt Males are affected more frequently than females

Etiology.—*The exact cause of such bony* changes is unknown Many theories have been proposed. Both Bamberger and Marie believe the bone changes were caused by a bacterial toxin Such an explanation would not account for the occurrence of this type of osteo arthropathy in congenital heart dis ease Others have suggested that the disease was due to prolonged venous congestion They reasoned that compression of the lung capillaries occurs in various pulmonary dis eases and that the resulting peripheral hyperemia was responsible for the bony changes This theory likewise fails to ex plain many cases Campbell believes that edema is the primary factor in every case of clubbing and postulates that such edema is the result of a chronic low grade anoxemia in tissues (fingers and toes) where the cir culation is slower This theory may well ex plain all cases of hypertrophic pulmonary osteo arthropathy and is worthy of further consideration

Morbid Anatomy —The most striking feature of the disease is the bulbous enlarge ment of the terminal phalanges of the fingers and toes, due largely to proliferation of the soft tissues The nail first becomes curved in both directions, the watch-crystal type of nail Its color and texture may be altered The parrot beak nail results because of in creased thickening and curving downward over the tip of the finger The tissues about the nail bed are puffed, smooth, reddened and the nail is felt to float The end of the finger, especially the nail bed is apt to be *cyanotic Rarely, the entire hand is enlarged* and pawlike Enlargement of the ungual phalanx is often seen in the roentgenograms

The process may become generalized, in volving the long bones of both extremities and occasionally the flat bones. Proliferation of the inner layer of the periosteum occurs early The proliferating tissue is readily cal cified and appears as an irregular layer of *new bone underneath the periosteum Most* commonly it affects the distal third of the diaphysis, although the entire shaft may be involved Roentgenologically, the bone appears to be surrounded by a shell Early in the disease it is readily differentiated from the original bone because of its poor lime content. Later it becomes so dense and so closely united that no line of de *marcation is demonstrable Occasionally* the entire bone may undergo a rarefying in flammation very similar to that of osteitis deformans although bowing never occurs and bone lengthening is rare Late in the disease the epiphyses may be similarly af fected Suppuration never occurs

The wrists knees ankles elbows and small joints of the hands and feet may be involved in the severe cases A low grade synovitis with an associated effusion can occur Actual ankylosis is rare

Symptoms —The *onset* is insidious In its simplest form clubbed fingers there are no symptoms Pain is invariably present when involvement of the long bones occurs It varies from a mild discomfort to a most distressing deep seated ache over the fore arms and legs It is often intermittent and may occur only at night or after long stand ing In most instances the bones are sen sitive to pressure Thickening of the soft tissues may ensue giving the distal half of the *forearm and leg a clumsy cylindric* appearance In well advanced cases the

joints are stiff and painful and at times swollen Enlargement of regional lymph nodes may be seen Kyphosis and rigidity have been observed The other associated symptoms and findings are usually manifestations of the primary disease

The *clinical course* is extremely variable but usually follows that of the primary disease. It has been known to appear and disappear rapidly (weeks) Exacerbations and remissions have been reported Repeated roentgenologic examinations show that absorption of the newly formed bone does take place The clinical course may be protracted lasting several years

Diagnosis —The clinical features of the disease are so distinctive that its recognition is rarely difficult.

Treatment—The therapy of hypertrophic pulmonary osteo arthropathy is essentially the treatment of the primary disease Symptomatic treatment of the skeletal and joint pains is often indicated and necessary

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ACHONDROPLASIA

(*Chondrodystrophia Foetalis*)

Definition—Achondroplasia a disease of the skeleton which begins in fetal life has the following characteristics a normal trunk a disproportionately large head pug nose dwarfed and curved extremities with trident shaped hands It is usually confined to bones which develop from cartilage although membranous bones may be affected directly or indirectly The various types described by Kaufman are probably variations of the same disease process

Incidence—The disease may or may not be hereditary Several achondroplastic dwarfs have been observed in one generation and the disease has been known to appear in successive generations In the case of *twins one may* be achondroplastic and the other normal It may be transmitted by either parent Males and females are affected with equal regularity

Etiology—Achondroplasia is the result of faulty development of the anlage for bone producing intermediary cartilage Ancon sheep Talemark and Dexter Kerry cows and the creeper fowl are excellent examples of achondroplasia, fixed by inheritance although *the mode* of transmission is *different* in each case Authorities are agreed that achondroplasia results because of anomalies in the germ plasm These anomalies are described as 'mutations by some and as chromosomal deficiencies or abnormalities by others

Morbid Anatomy—The general deformities are unique The fetus is a dwarf with *an average length of 30 to 40 cm* as contrasted with the normal 50 cm The head is relatively large (brachycephalic type), with pug nose appearance, prominent lower jaw thick lips and thick protruding tongue The circumference of *the head may* equal or exceed the body length The trunk is well developed but the extremities are short, although usually well formed (micromelia) In consequence the central point of the body is at the xiphoid instead *of the* symphysis pubis as normally The hands are small and pudgy All of the fingers are tapering of nearly equal length and spread like the spokes of a wheel (main en trident) A striking peculiarity is the general thickening of the skin over the whole body and a folding especially over the joints

Of the individual bones those usually affected in order of frequency are the femur humerus tibia fibula radius ulna *pelvis* base of the skull bones of the hands and feet vertebrae and ribs The long bones appear short thick and hard The natural curves are exaggerated The cortex is often thick because of excessive periosteal proliferation The epiphyses may be of normal size or enormously hypertrophied giving the ends of the bones a mushroom like appearance In achondroplasia periosteal ossification may

be normal or increased whereas endochondral ossification is defective The most characteristic microscopic finding is aplasia or dysplasia of the proliferative zone of cartilage As a result of the absent or defective endochondral ossification and the normal or increased periosteal ossification bone growth and bone structures are grossly altered Synostoses in the skull pelvis and other bones are common

Symptoms.—The symptoms are largely objective and have already been described A vast majority of the infants with this disease are stillborn death occurring from the seventh to the ninth month of uterine life. The few who survive are subjects of this peculiar and characteristic type of micromelic dwarfism which does not interfere with either mental or sexual activity or longevity The fetal abnormalities of the skeleton are never altered A peculiar feature of the disease is the abnormal development of the skeletal muscles which gives the subject a strength relatively much greater than that of a normal individual Mentally the achondroplastic dwarf is rarely subnormal The sexual organs in both sexes show a normal or exaggerated growth. Sexual precocity is not uncommon, and sexual desire is said to be excessive

The roentgenologic findings are very striking The long bones are short, stubby wide at their ends and much more dense than normal The excessive periosteal ossification may encroach upon the medullary space The ridges where muscles attach are considerably increased. A peculiarly characteristic deformity of the affected bones is the abrupt expansion of the epiphyseal end where ossification is irregular and defective Localized bowing especially in the tibia and femur is usual The ribs may show various thickenings deformities and at times enlargement of the costochondral junctions The vertebrae may be wedge-shaped or irregularly developed The time of appearance of the ossification centers varies greatly as does the time of union of the epiphysis and diaphysis.

Diagnosis—The unique features of achondroplasia mentioned above should serve to differentiate it from other types of skeletal disease

Prognosis—The majority of achondroplastics die in utero Those who survive the first year may reach extreme old age They rarely exceed 140 cm in height.

Treatment—No known treatment affects the disease Deformities when present can be corrected by surgical procedures

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OXYCEPHALY

(Acrocephaly Tower Skull Steeple Head Scaphocephaly Keel- or Boat-Shaped Head)

Definition—Oxycephaly is a constitutional anomaly associated with premature closure of the cranial sutures and resulting deformity of the head The tower shaped head with associated exophthalmos adenoid facies partial or complete blindness represents one of the results of such premature synostosis. The scaphocephalic head with bulging frontal and occipital regions is however the most frequent expression of this constitutional anomaly

Incidence.—The exact incidence of premature synostoses has never been established The disease begins in fetal life more commonly affects males and rarely occurs in more than one member of a family The hereditary nature of the disease has been clearly demonstrated in rabbit breeding experiments In such animals the synostoses appear in the third week of uterine life

Etiology—Most workers agree that the interstitial mesenchymal tissues are primarily at fault in producing premature synostosis The misplaced centers of ossification and hypoplasia of the base of the skull are considered secondary changes

Morbid Anatomy—The pathologic changes are limited to the skull except in the occasional case with associated congenital defects The most striking features are the absence of the frontal and occipital bossae with displacement of their centers of ossification into the synostosed sutures The coronal suture may be completely synostosed or only the lateral thirds may be involved The sphenoid bones are broader than normal The orbital openings are enlarged but the orbital cavities are reduced in size Occasionally the optic foramina are narrowed The maxillae are hypoplastic The sinuses are small, rudimentary or absent. The base of the skull is hypoplastic, the fossae being shorter and deeper than normal The sella turcica is usually unchanged The bones are thin, the diploe small and the inner table may be absent Hyperostosis is seen occasionally The brain is of normal volume but tower shaped The convolutions are usually flattened Although optic neuritis and atrophy are invariably present the other cranial nerves are normal Bilateral and symmetric syndactylism usually of the upper extremities may be present Polydactylism anomalies of the elbow and malformation of the ears are seen In scaphocephaly synostosis of the sagittal suture occurs The head although less deformed is keel or boat shaped

Symptoms—The oxycephalic head is most unique in appearance The high flat forehead slopes gradually upward to the vertex with ill defined superciliary ridges and glabella The shortness of the head is as characteristic as its height being due chiefly to the reduction of the occiput which may be even with the neck The hairy scalp may be raised above the normal level appearing as though it were perched on top and as a result the ears appear lower The characteristic mouth breathing gives the patient a weird vacant stupid expression The exophthalmos is a constant feature The degree of protrusion varies greatly actual dislocation having been noted Lacrimation conjunctivitis and divergent squint are common Nystagmus is seen occasionally Marked visual defects, increasing with age are frequent A postneuritic type of optic atrophy is seen in one third of the cases and is almost always present in the adult It may occasionally be unilateral Blindness occurs in 10 per cent of these patients Malocclusion of the teeth with a high, narrow hard palate is seen frequently Partial cleft palates are encountered occasionally The senses of smell and taste are preserved A mild to moderate degree of increased intracranial pressure is often present Headaches are common, often severe in nature Convulsions may occur Mental retardation is noted in about 20 per cent of these patients Some retardation of growth and development may or may not be present The disease has no effect on the duration of life

Treatment.—Little can be done for this disease Cranial decompression may aid in arresting the visual defects and in combating the symptoms of increased intracranial pressure The associated malformations may require surgical treatment for functional or cosmetic reasons

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LEONTIASIS OSSEA

(Hyperostosis of the Skull Megalocephaly Fibromatosis Osteoplastica Ossium Hyperostose des Os de la Tete)

Leontiasis ossea is a rare disease first described by Malpighi in 1697 It was not called *leontiasis ossea* until 1864 when Virchow published a more complete description of the disease This name was chosen because the bony overgrowth corresponded with the overgrowth of connective tissue seen in molluscum fibrosum with leonine *facies* The chief feature of the disease is hyperostosis of the bones of the skull The process *may* be limited to one bone or involve all of them In advanced cases marked *facial deformities*

may result but not of the type suggested by the name. Skulls weighing more than 4000 Gm with the thickness of the calvarium measuring 2 inches or more have been reported A few cases have been reported with involvement of some of the long bones

Etiology—The cause of the disease is unknown The data presented in favor of the various infectious, traumatic metabolic and endocrine theories are wholly inadequate Because the pathologic process may resemble that of Paget's disease, some have considered it to be a localized form of osteitis deformans The occasional case of leontiasis ossea with long bone involvement would favor such a view The disease begins in childhood or early adolescence Females are more commonly afflicted

Morbid Anatomy—The process may involve one or all of the bones of the skull Knaggs describes both the creeping periostitis and the diffuse osteitis type The histologic changes are the same in both except for the large deposits of subperiosteal bone in the periosteal type Early in the disease one notes disappearance of the usual bony structures The outer layers are less compact and areas of bone dissolution appear filled with vascular and fibrous connective tissue which may subsequently become fibrosed New bone may be laid down in irregular fashion in such fibrous areas although neither the laminations nor the haversian systems of normal bone are formed Small cysts may remain In the later stages the bone loses its normal contour and is greatly thickened and porous When suppuration is present it is the result of secondary infection Isolated bone sections may resemble either Paget's disease or osteitis fibrosa cystica except that the fibrosis is more marked in leontiasis ossea

Symptoms.—The symptoms are dependent on the size and shape of the bones involved If limited to one bone the facial appearance may be grotesque The symptoms are subjective and the direct result of pressure Headache may be an early and at times a severe symptom Exophthalmos is nearly always present Visual and hearing defects neuralgia paralysis and dilatation of veins are frequent. Obstruction of the nares and lacrimal duct may be observed Insomnia, mental dulness and convulsions may appear The course of leontiasis ossea is usually from twenty to forty years Death may occur suddenly with a convulsion More commonly it is due to cachexia.

Roentgenologically one observes a marked increase in the bone density Later the process may appear more translucent or fluffy The long bones should always be x rayed in order to be certain that Paget's disease has been ruled out

Diagnosis—Except in the early cases diagnosis is rarely difficult The facial deformity is more like that encountered in Paget's disease involving the facial bones however the patient is usually a child or adolescent.

Treatment—This is restricted to surgical procedures to relieve pressure

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FRAGILITAS OSSIUM

(Osteogenesis Imperfecta Osteopsathyrosis Brittle Bones and Blue Sclerae Lobstein's Disease Hereditary Hypoplasia of the Mesenchyme)

Definition—Fragilitas ossium is a rare congenital disease of the skeleton characterized by frequent fractures of bones dwarfism deformities of the head chest and extremities The disease begins in fetal life but rarely manifests itself before infancy childhood or early adolescence Blue sclerae relaxation of ligaments dislocation of joints and otosclerosis (after the age of twenty) are commonly encountered in the hereditary type The nonhereditary type may or may not have associated blue sclerae

Etiology.—Most workers are agreed that the disease is the result of a hereditary hypoplasia of the mesenchyme the exact cause of which is unknown The disease more commonly affects females and the female is the more potent transmitter The inheri

tance factor follows the mendelian law and appears as a dominant characteristic De spite the renewed interest in the thymus, no one has demonstrated that dysfunction of this gland occurs in fragilitas ossium Failure to demonstrate any abnormality of the serum calcium and phosphorus and of the calcium excretion excludes the parathyroid gland from playing an etiologic role in this disease Slight inconstant unexplained elevations of the serum phosphatase have been observed

Morbid Anatomy—The bone deformities are directly proportional to the severity of the disease and to the frequency of fractures In extreme cases the calvarium is soft, with only islets of calcified tissue, and the long bones are grossly deformed in consequence of numerous fractures In the milder cases without fractures, the long bones are unusu ally slender but approximately normal in contour The fractures heal readily and may be found in all stages of repair The cortices are thin and usually, only a few fragmentary trabeculae are seen Osteoclasts appear nor mal in number but osteoblasts are greatly reduced The haversian canals are unusually wide The epiphyseal cartilage is usually nor mal Rarely the zone of provisional calci fication shows retarded activity The connec tive tissues throughout the body may be more delicate and friable the tendons being small the blood vessels and periosteum quite friable and the sclerae thin and translucent The thin, translucent sclerae allow the un derlying choroid vessels to shine through im parting the characteristic blue appearance

Symptoms—Individuals affected with fragilitas ossium tend to be shorter than normal Constitutional symptoms are absent The shape of the head is often a striking feature Protuberances of the occipital and frontal regions are common features A bitemporal protuberance so marked as to turn the ears outward has frequently been described The sclerae tend to have an ab normally blue color varying from a robin s egg to a deep slaty blue The disease is usually not suspected until fractures have occurred Marked fragility of the bones and the deformities caused by numerous frac tures constitute the chief features of the disease They usually appear in early child hood following slight violence Their fre quency is directly related to the severity of the disease and the activity of the patient

The congenital type is the most commonly encountered and severest type Such cases develop fractures and deformities in utero They are usually stillborn or die soon after birth If they survive they are helpless crippled dwarfs The patients affected with the infantile type appear normal at birth and experience their first fracture when they begin to stand and walk Greenstick frac tures without pain are common The degree of deformity present depends on the num ber of fractures their appropriate treatment and prevention The tarda type manifests itself in childhood or early adolescence frac tures occurring at the slightest provocation Otosclerosis never appears before the third decade

The roentgenographic features are marked generalized osteoporosis and slender, long bones of reduced diameter with thin cortices The bony structure may be unusually prom inent with trabeculae readily seen The epiphyses although smaller than normal appear expanded because of the narrow diaphyses The calvarium is unusually thin Islets of calcification may be demonstrable

Prognosis—The congenital type is born dead or dies shortly thereafter Those who survive are handicapped all their lives In the infantile and tarda types fractures be come less frequent with increasing age. Those patients who are carried through adolescence with little or no deformity can be expected to lead a fairly active life They should be told that the disease is transmitted as a dominant characteristic, and that if they have children approximately one half of them may be expected to develop the dis ease

Diagnosis—A typical case of fragilitas ossium rarely presents any serious diagnostic problems Because of short extremities an occasional case may be momentarily con fused with achondroplasia The large head pug nose short extremities and trident hands of the achondroplastic are of them selves diagnostic The roentgenologic dif ferences are striking Rarely a case of rickets occurring at one year of age with curvatures and fractures might be confused with frag ilitas ossium The absence of other signs and the dietary history should serve to dif

ferentiate the two Rarely should it be necessary to resort to chemical and x ray studies

Treatment —There is no known specific therapy Vitamins lime salts and various endocrine preparations have been administered without effect Elementary phosphorus has been employed with resulting sclerosis of the growing ends but without effect on the cortices where calcification is most needed Stramonium lactate followed by tricalcium phosphate and vitamin D has been employed without benefit Estrogenic therapy has caused an increased retention of calcium and phosphorus in several carefully studied cases Whether the effect of such therapy is sufficient to make its administration of practical clinical value it is as yet too soon to say It is obvious that every precaution should be taken to avoid fractures and that when they do occur they should be treated promptly if deformities are to be prevented The eyes never require treatment There is no treatment for otosclerosis.

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OSTEITIS DEFORMANS

(Paget s Disease)

Definition.—Osteitis deformans is a chronic disease of the adult skeleton characterized by hypertrophy and bowing of the long bones and irregular deformation of the flat bones Our knowledge of the clinical aspects of the well advanced classic form of osteitis deformans has not increased greatly since the masterly description written by Sir James Paget in 1876 The introduction of roentgenologic and biochemical examinations into clinical medicine has contributed to our understanding of the disease in its early stages particularly the monostotic and localized forms

Incidence —Osteitis deformans is one of the more common affections of bones in adult life, occurring most frequently in the fourth fifth and sixth decades of life Schmorl reported a postmortem incidence of approximately 3 per cent in persons more than forty years of age It is rarely seen under thirty years of age In fact no authentic case under twenty five years of age has been recognized Males and females are about equally affected In Gutman's series of one hundred sixteen cases the sex incidence was the same Occasionally Paget s disease occurs in more than one member of a family A family in which three siblings and their mother were so afflicted has been reported

Etiology —The disease has been considered a clinical entity since Paget s classic description appeared and in consequence the disease bears his name He concluded that it was 'a form of chronic inflammation of the bones" The preponderance of clinical biologic and pathologic data does not favor its being a generalized systemic disease of either infectious or endocrine origin The prevailing opinion appears to be that Paget s disease is the result of some local disturbance in bone metabolism the exact nature of which is unknown

Morbid Anatomy —In osteitis deformans the changes may be confined to a portion of one bone and as Schmorl pointed out though often polyostotic it is rarely generalized The pelvis skull femur humerus lumbosacral spine tibia and dorsal spine are most commonly involved No bone is exempt The characteristic changes of the long bones are increased thickness sometimes of considerable degree varying grades of bowing and lengthening Their general contour may be irregular and their surfaces uneven Similar changes are seen more frequently in the skull than in the other flat bones The bones may be sufficiently soft to be cut with a knife On section they vary greatly in appearance As a result of new bone formation internally and on the surface the cortex increases in diameter while

the marrow cavity becomes narrowed or obliterated In some regions the bone may appear coarsely trabeculated and spongy, with evidence of an increased blood supply In other regions the bone is dense and ivory like Small bone cysts may be seen The extent and severity of the disease are not necessarily related to its duration Extensive arteriosclerosis is almost always present but is not the cause of the bone changes

Microscopically one sees an obviously disordered bone architecture There seemingly exists an imbalance between the factors which normally control bone formation and bone resorption both of which are accelerated In most instances bone formation is in excess of bone resorption although occasionally one finds regions where the first manifestation is an increased osteoclastic activity Hyperplastic vascular connective tissue may completely fill such areas Subsequently new bone is formed in an abnormal pattern The new bone may be laid down on old, partly eroded trabeculae or may enter into the formation of new ones which run in all directions The altered bone of Paget s disease takes on a distinguishing mosaic appearance because of the irregular configuration of the trabeculae and the numerous, thick uneven dark staining cement lines

Symptoms—The symptoms of osteitis deformans vary greatly In approximately 25 per cent of the cases no symptoms or signs are complained of at the time the diagnosis is made In such instances the disease is usually discovered accidentally during the course of a roentgenologic examination A large proportion of such patients have fairly extensive Paget s disease even though the disease was not suspected by the patient or the examining physician The localized and the monostotic forms are often discovered accidentally The sites most commonly affected by this form are the end of one shaft (the remainder being normal) the ischium, pubis ilium sacrum or a vertebra

In those patients complaining of symptoms, the onset is usually so insidious that it is impossible to determine when the disease began Many such patients do not seek medical aid until years later General and constitutional symptoms are rarely encountered Weakness and fatigability may be complained of by patients with deformities of the lower extremities Pain is the most common and usually the first subjective symptom varying in character from a dull soreness to the most intense paroxysmal type It may be worse after walking or standing and is relieved by rest It may occur at night It is usually in the region of the bone involvement but may be generalized The pain may disappear spontaneously The tissues overlying some of the involved bones may exhibit redness and increased temperature on palpation Pressure over such areas may result in exquisite pain Joint pain and stiffness are sometimes present Intense muscle pain and spasm are common accompaniments of the deformities Muscle atrophy ultimately develops Spontaneous fractures occur and may be the first cause for complaint. Pain in the head varying from a dull ache to severe neuralgia is complained of by some, yet others with obvious involvement of the skull have no such complaints Impairment of hearing is a common complication, impaired vision is much less frequent Sarcomatous degeneration has been reported to occur in as high as 10 to 15 per cent of the cases in one large series (one hundred sixteen cases) none was seen Renal calculi are occasionally encountered

The disease may begin in any bone The skull and the tibiae are frequently the site of onset However bowing of the tibiae as the first sign of Paget's disease has been greatly overemphasized In well developed cases the picture is a very striking one The whole calvarium is much enlarged the head is carried forward with the chin almost resting on the chest and the movements of the head are greatly restricted The spine is bent markedly forward and is rigid the bones of the shoulder girdle are massive the thorax is compressed laterally, the pelvis is very broad and massive, the legs are bowed forward and outward The arms may likewise be bowed the upper arm forward and the forearm outward and forward A marked flexion of the trunk on the legs compensates for their bowing and permits maintenance of equilibrium As a result of the deformities there is a considerable reduction in stature often as much as 6 inches On stand

ing, the feet are markedly everted one being a considerable distance in front of the other The gait is labored and waddling

The most characteristic roentgenographic features of osteitis deformans are increased bone density and loss of normal architecture The roentgenologic appearance varies with the stage of the disease Early the bone may be much less dense than normal Some of these areas of decreased density appear spotty or cystic in character and the neighboring bone is of increased density Such areas, which may involve only a portion of a shaft or the skull subsequently take on the characteristic of well advanced Paget s disease. In this stage of the disease the cortices are greatly thickened and the marrow cavity is narrowed or obliterated The bone, although dense tends to appear mottled or shows the characteristic coarse trabeculations The margins of the bones particularly those of the skull, appear fuzzy and indistinct. In consequence of the marked bowing numerous incomplete fractures of the convex aspect are often present The uninvolved bones are *normal.*

The course of Paget's disease is most variable The more severe and extensive cases may result in complete crippling in twenty to thirty years The disease may become arrested or quiescent This is true of all types but more so of the localized and monostotic forms

The changes in the calcium and phosphorus metabolism observed in osteitis deformans are not of the type observed in hyperparathyroidism. The serum calcium is normal and the serum phosphorus only slightly increased or normal The serum phosphatase is always increased being much higher in osteitis deformans than in hyperparathyroidism with a comparable degree of bone involvement The phosphatase values vary with the activity and severity of the disease the slightest elevations being associated with the localized forms In some cases the excretion of calcium and phosphorus is increased but such increases are not confined solely to the urine as they are in hyperparathyroidism

Diagnosis.—The roentgenologic appearance of even the early localized forms of Paget s disease is so characteristic that there is rarely any question as to diagnosis

Osteoblastic skeletal metastases secondary to carcinoma of the prostate may be impossible to distinguish, roentgenologically, from Paget s disease The serum phosphatase in such cases may be as high as in extensive Paget s disease Careful urologic study will usually enable one to make the correct diagnosis

Hyperparathyroidism.—Rarely should Paget s disease be confused with or mistaken for hyperparathyroidism, particularly in the advanced stages Consideration of the previously mentioned clinical, biochemical roentgenologic and pathologic differences should make the diagnosis relatively easy in the questionable case A few cases of hyperparathyroidism simulating or complicated by osteitis deformans have been observed

Leontiasis ossea begins in childhood is confined to the skull and rarely involves any other portion of the skeleton The serum calcium phosphorus and phosphatase values are normal

Bowing of the legs under forty years of age is rarely due to osteitis deformans. The development of such deformities in later life should always suggest the disease

Rarely if ever should multiple myeloma osteomalacia senile osteoporosis and other skeletal diseases associated with decalcification be confused with osteitis deformans Their diagnosis is discussed under Osteomalacia page 1318

Tertiary syphilis of the bone luetic periostitis osteopetrosis melorheostosis hyperostotic meningiomas neurofibromatosis yaws of the bone sclerosing osteomyelitis osteogenic sarcoma and acromegaly rarely simulate osteitis deformans other than superficially and their differentiation from Paget s disease should never be difficult In any doubtful case the diagnosis can be established by roentgenologic examination or by examination of a biopsy specimen.

Treatment.—There is no specific treatment for osteitis deformans Parathyroidectomy should never be performed Schmorl was unable to demonstrate any significant histologic changes in the parathyroid glands of one hundred thirty eight cases The administration of parathyroid extracts and acid salts is contraindicated Suprarenal extracts are without effect. Roentgen ray

therapy to the affected bones may relieve pain although often temporarily The best results are obtained when the disease is confined to the nonweight bearing bones Slitting of the periosteum relieves the tension of the periosteum and in most instances the pain We routinely administer a high calcium, high vitamin diet with added calcium glycerophosphate (doses of 3 to 6 drachms per day) 10 000 to 20 000 units of vitamin D and 50 to 100 mg of cevitamic acid in the hope that new bone formation can be kept greatly in excess of bone absorption

Orthopedic measures such as exercises for muscle atrophy and built up shoes in the case of leg shortening are often necessary Fractures should be treated as if the bones were not diseased They heal in a normal manner except that calcification of the callus may be delayed If a sarcoma should develop it should be treated radically with the hope that metastases may be prevented Hearing appliances are often necessary

WALTER BAUER

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SENILE OSTEOPOROSIS

(*Idiopathic Osteoporosis Postmenopausal Osteoporosis*)

Definition —Osteoporosis occurs in every aging and senile person hence the derivation of the term senile osteoporosis This designation has never been satisfactory because many individuals exhibiting osteoporosis without obvious cause are neither aged nor senile nor did the introduction of the term idiopathic osteoporosis frequently used in referring to this latter group enlighten us The recently coined name postmenopausal osteoporosis,' is most appropriate because the disease generally affects women after the menopause and estrogen therapy induces calcium and phosphorus retention in the subjects so afflicted

Incidence —From the foregoing it is apparent that all elderly people, particularly women are most frequently affected The average age in three reported series has been fifty seven sixty two and sixty six. However if the menopause is artificially produced the disease may appear at a much earlier age in one instance the first symptoms were experienced at the age of forty two The sex incidence is striking forty of the forty two patients studied by Albright and one hundred sixty seven of the two hundred eight cases reported by Black were women

Pathogenesis —The etiology of senile osteoporosis cannot be discussed without first describing its pathogenesis and depicting this necessitates defining the term 'osteoporosis' Adult bone is composed of an organic matrix in which is embedded a calcium phosphate carbonate complex Normally the two surfaces of the trabeculae are continuously subjected to two processes the one by resorption the other by formation The former is a function of the osteoclasts the latter is governed by osteoblasts Bone may be deficient because resorption is too great or because deposition is impaired Resorption is the result of increased osteoclastic activity which if continuous leads to osteitis fibrosa generalisata The formation of too little bone may be due to either failure of the osteoblasts to lay down sufficient osseous matrix or because the matrix once laid down is not calcified The former condition is osteoporosis the latter osteomalacia or rickets Accordingly it is emphasized that osteoporosis is primarily a disorder of tissue metabolism failure of the osteoblasts to lay down sufficient matrix and only secondarily a disease of calcium and phosphorus metabolism It is this abnormality with which we are concerned

Etiology —The extremely high incidence of osteoporosis in women, its constant tendency to appear after the menopause and the striking retention of calcium and phosphorus which ensues in this condition when estrogenic material is administered led Albright and his co workers to conclude that the postmenopausal state is the commonest etiologic factor in most cases of senile and idiopathic osteoporosis Whether the male climacteric results in the same sequence of events remains to be proved If it does the resulting osteoporosis proceeds more slowly Atrophy of disuse may be a contributing factor especially in those individuals who lead sedentary lives or are immobilized for a time because of vertebral fractures or other causes That faulty diet plays a role has not been established It is conceivable that if calcium and phosphorus are readily available the resorption of bone might be lessened This latter hypothesis would explain the beneficial effects observed in the treatment of patients with osteoporosis by means of high calcium high phosphorus diets and large amounts of vitamin D Albright suggests that a diet deficient in protein may play a more important etiologic role than one low in calcium and phosphorus because the former might result in a negative nitrogen balance and thereby make it difficult or impossible for the osteoblasts to lay down the necessary osseous matrix the prerequisite to bone formation That senescence plays a role cannot be denied

The serum calcium phosphorus and phosphatase levels are normal This is as it should be if osteoporosis is a disorder of tissue metabolism and not a primary disease of calcium and phosphorus metabolism However the urinary calcium and phosphorus excretion may be increased early in the disease This is not surprising because normally some of the calcium and phosphorus set free by the process of resorption is deposited in the newly formed osseous matrix. In osteoporosis this calcium and phosphorus are excreted because bone formation is impaired However once the decalcification is marked less calcium and phosphorus are derived from resorption and the urinary excretion is again normal or may be reduced

Morbid Anatomy.—The conditions operating to produce senile osteoporosis are those related to the production of the general involutionary process of aging Pommer was the first to demonstrate that normal bone formation was decreased while normal resorption continued with the result that progressive thinning of the bones occurred Therefore, late in the disease certain gross skeletal changes such as dorsal kyphosis and fractures of the vertebrae and the neck of the femur are frequently seen Grossly *one observes thinning of the cortices thinning* and absence of the trabeculae and fatty atrophy of the marrow Microscopically, the osteoid borders are not demonstrable or barely so, osteoblasts are diminished in number or hypoplastic and osteoclastic activity is unaltered

Symptoms.—The symptoms of osteoporosis are directly proportional to the severity of the disease the latter being governed by the rapidity with which the involutionary changes occur and the presence or absence of other factors As might be expected some of these patients are symptom free In such instances the disease is accidentally discovered during the course of x ray examinations made because of some other malady The average period of onset of symptoms following the menopause is between nine and fifteen years being later in women whose menopause has been induced artificially

The usual history is a woman in her fifties eight to fifteen years after the menopause experiences a sudden snap or pain in the back as a result of a jolt fall lifting or bending If an x ray examination is made at this time the disease is apparent Crushed or fractured vertebrae frequently result from such minor accidents The back pain persists and any sudden movement tends to cause sharp darting pains often radicular in character There is usually a previous history of weakness fatigue and various skeletal aches and pains Urinary calculi may occur in consequence of the initial hypercalcinuria and hyperphosphaturia These patients tend to show atrophy of skin and other tissues and dorsal kyphosis may be present

Roentgenograms disclose that postmeno*pausal osteoporosis has a predilection for the* spine and pelvis However the long bones

are involved in the more severe forms of the disease The skull is rarely affected, an important point in differentiating this type of osteoporosis from that due to other causes particularly, hyperparathyroidism The x ray films of the spine reveal decalcified vertebrae of the so called fish vertebrae type particularly in the lower thoracic and lum bar regions The additional pathologic lesions seen consist of crushed or fractured vertebrae herniation of the nucleus pulposus through the end plates of the vertebrae (Schmorl s nodes or Knoetchen) and frac tures of the neck of the femur

Diagnosis—This should rarely present *any difficulty* The patient *usually* a woman some ten years after the menopause first *notes the previously mentioned symptomat* ology Clinical studies reveal an osteoporotic *spine and pelvis with little or no evidence* of decalcification elsewhere normal serum calcium phosphorus and phosphatase levels and normal or slightly increased urinary calcium and phosphorus excretions Any of the skeletal diseases characterized by gen eralized decalcification may be confused with postmenopausal osteoporosis Their diagnostic features are discussed under osteomalacia (p 1318)

Treatment—To date the treatment of osteoporosis has been most unsatisfactory despite claims to the contrary Whether the previously mentioned effect of estrin on the calcium and phosphorus balance is sufficient to make its *administration of practical clin ical* value remains to be seen Daily intra *muscular injections* of 1 66 mg of estradiol benzoate for a period of ten days cause a marked retention of calcium and phos phorus However restoration of the normal calcium content of an osteoporotic skeleton would require years of therapy If estrin is administered it should not be given continu ously In order to take advantage of the possibility of lessening bone resorption by having calcium and phosphorus available in increased amounts a high calcium high phosphorus diet and large amounts of vita min D are advised Such a diet should con tain at least 1 Gm of calcium per day This is readily furnished by partaking of generous amounts of milk cheese and eggs Ten to fifty thousand units of vitamin D per day in the form of cod liver oil or one of the potent vitamin D concentrates will suffice The relief of pain is best obtained by assum ing the recumbent position increasing the tone of the musculature of the back by means of exercises and supporting it when necessary with a light brace Heat and mas sage are effective in combating the pain and muscle spasms accompanying *the acute* episodes Prolonged immobilization should *be avoided whenever possible in order to* prevent the osteoporosis of disuse from caus *ing further demineralization*

WALTER BAUER

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DISEASES OF THE NERVOUS SYSTEM

INTRODUCTION—METHODS OF EXAMINATION

It is impossible to understand nervous diseases without comprehension of general medicine and general pathology The number of primary diseases of the nervous system is rather small and degenerations due to defective hereditary endowment or vital lack are unpromising material for treatment Infections such as the acute exanthemata poliomyelitis, syphilis or tuberculosis however may exert their most serious effect on the brain or spinal cord and vascular degeneration is the cause of such simple and common brain lesions as apoplexy and cerebral thrombosis. Even central softening of the cord may be produced by sclerosis of spinal arteries if it be so severe as to impair nutrition of spinal nervous elements The accurate appraisal of the powers of a failing heart muscle or the discovery of a starch indigestion may be the clue to the cause of senile epilepsy and a high nonprotein nitrogen content in the blood may throw light on obscure conditions such as recurring convulsions The presence of hematoporphyrin in the urine may be evidence that an apparent nervous breakdown' in an overworked middle aged banker is really a chronic acetanilid poisoning from bromo seltzer potation and a high sugar content in the blood although the urine is normal may reveal the diabetic character of certain multiple neuritic and radicular pains which were previously unidentified and therefore irremediable Neuritis of the brachial plexus is more often due to toxic absorption from a periapical dental abscess than to exposure to cold Absence of free hydrochloric acid in the gastric contents gives a lead to the correct therapy of pernicious anemia and combined system disease of the spinal cord in the fourth and fifth decades of life The physician bent on correct neurologic application must therefore like St Peter on the roof top call nothing common or unclean in his search for prime causes and if he cannot culture the stool himself must be aware of cultural possibilities and their significance Just as a student must master a technic in order to diagnose a chest condition must understand how to inspect to percuss, to auscultate and to weigh the positive and negative signs thus discerned, so he must know a simple method of approaching a neurologic problem an irreducible minimum of examination to be systematically pursued which is based as all examinations must be on accurate anatomic and physiologic knowledge.

It is not necessary to elaborate here the details of these fundamental sciences, but a plan of clinical approach may be outlined with such application of our knowledge of structure and function as may be needed for illumination

I. General impression. Attention Memory Emotional state Delirium Coma Drowsiness

II Nervous system.

- (*A*) Organic.
  - 1 Cranial nerves
    - 1—Sense of smell in each nostril coffee, peppermint, etc
    - 2—Vision acuity fields fundi, scotomata
    - 3—4—6—Pupils reaction regularity of outline ocular movements diplopia, strabismus nystagmus
    - 5—Motor sensory including cornea
    - 7—Muscles of expression voluntary and emotional movements of face
    - 8—Cochlear acuity tinnitus Vestibular Bárány tests etc
    - 9—10—11—12—Movements of tongue, palate sternomastoids trapezii, articulation
      - Deglutition gag reflex tongue tremor
      - Cords laryngoscope
  - 2 Motor status
    - (*a*) Head attitude, tremor etc.
    - (*b*) Upper extremities power at each joint (grip with dynamometer)
      - Tone muscular nutrition Adventitious movements Tremor
      - Athetosis Fibrillary twitching Coordination including deviation test Speech type of handedness

(c) Trunk power of abdominal wall muscles
Umbilical excursion
(d) Lower extremities as in upper extremities with addition of station and gait
(e) Fits jacksonian or generalized

3 Reflexes superficial corneal palatal epigastric, abdominal bulbo cavernosus plantar
Deep jaw wrist, elbow knee and ankle Ankle and patellar clonus
Organic Micturition retention retention with overflow incontinence Periodic automatic incontinence Defecation control Priapism Sexual potency Urethral and anal sensations during sphincter relaxation

4 Sensory status subjective pain direction of radiation character frequency
Headache tingling
Sensibility to touch pain temperature deep pressure pain sense of position at joints Vibration sense Stereognosis All abnormal areas to be charted pictorially

5 Trophic functions skin bullae herpes bed sores perforating ulcers
Glossy skin erythema Hydropathies

(B) Vegetative nervous system
Cervical sympathetic dilation of pupils to shade
Ciliospinal reflex proptosis exophthalmos enophthalmos retraction of upper lid pseudoptosis
Flushing or sweating angioneurosis Raynaud s disease
Erythromelalgia transient edemata Localized sweating

III Skeletal system Abnormal projections and depressions
Tenderness on percussion immobility of spinal column
IV Gastro-intestinal system
V Respiratory system
VI Cardiovascular system with blood pressure etc
Temperature pulse
VII Glandular system
VIII Laboratory data blood and spinal fluid
Summary
Tentative diagnosis

History—The general character of the complaint should first be determined so that the examiner may be oriented to some degree, as to the nature of his problem then a more careful history of the beginning and progress of the symptoms which has led up to the final condition This must be obtained as far as possible in chronologic sequence and should be as fully elaborated as the patient will permit Some cross examination is usually needed and leading questions may be delicately suggested, for example transient attacks of diplopia or of inadequacy of the bladder sphincter, remote in point of time, usually must be sought after and similar direct questions often have to be made depending on how the trend of the history stimulates the diagnostic ideas of the examiner The *position* of a lesion of the central nervous system is often determined by clinical examination which reveals precisely the nature and degree of the loss of physiologic function but its *nature* frequently can only be surmised by careful consideration of the manner in which such functions are interfered with Four patients for example suffering respectively from luetic spinal thrombosis, extradural fibroma Pott's disease (tuberculosis) and spinal fracture dislocation, all of which have involved to a severe degree the tenth dorsal segment of the cord, should have practically identical clinical manifestations and disabilities, spastic paraplegia (paralysis of both legs with increase in muscle tone), complete sensory loss below the level of the affected spinal segment and sphincter paralysis These can be readily differentiated by the variations in anamnestic detail Complete paraplegia in the first instance would occur painlessly as an acute or subacute process lasting but perhaps half an hour In the second probably one lower extremity would have symptoms sensory and motor for months before the other was involved and even then complete paraplegia would probably take place slowly and be accompanied possibly by radicular pains confined to the skin area supplied by the tenth dorsal roots In the third case severe localized and shooting root pains would preface for a long time the rapid onset of signs of paraplegia These pains are ameliorated by rest and increased by movement during the months in which the disease is confined to the bone and before the collection of inflammatory exudate so compresses the cord as to forbid transmission of impulses The history of injury in the last instance would of course almost certainly reveal the cause of the paralysis

Examination—After the previous personal and family history have been taken, the above scheme should be followed in the further conduct of the examination but

with discrimination for one naturally does not examine visual acuity and the sense of smell before determining the picture in broader outline by appraising the proper functioning of the more important cranial nerves and the motor reflex and sensory systems It is usually wise to leave the ex amination of sensation to the last because the condition of the other systems capable of more rapid investigation may indicate the probable character of the sensory derange ment.

During the entire examination facts are gradually revealed which guide the physician toward this diagnosis or that Consequently it is possible to stress some parts of the pro cedure more than others, to discover the futile lines of investigation and to make the examination more forceful in other direc tions Proper incidence in examination can only be learned by experience, and the student would do well at first to master the routine method already set forth

The *mental functions* can be roughly judged by the taking of the history The power of attention and concentration may be more precisely gauged by some such test as Bourdon s in which the patient is asked to mark on a printed page a certain letter or letters. Should a suspicion arise of the patient s mental endowment Ziehen s tests may be employed Simple problems such as explaining the difference between a river and a lake water and ice an error and a false hood or further the Binet Simon or Terman scale may be employed with wisdom

Nervous System.—The *first* and *second cranial nerves* are really parts of the brain and not peripheral nerves but it is conveni ent for clinical purposes to regard them as such Visual acuity is tested roughly by asking the patient to count fingers with each eye separately Accurate tests are made with Snellen s types and pictures Changes in the size of the fields of vision can be determined roughly by seeing if the patient has as large a field of vision as that of the examiner for accurate measurement a perimeter is necessary

By *hemianopia* is meant blindness of half the visual field due to a lesion at the optic chiasma or behind it in one of the optic tracts *If the lesion be in front of the* chiasma *e g* in the optic nerve itself no hemianopia occurs because *the decussation* of the optic fibers has already taken place Ipsolateral blindness results with optic atrophy expressed by an optic disk white as tissue paper when seen with the ophthal moscope Such lesions of the optic nerve may be due to glioma of the nerve or to *pressure on the nerve* by a subfrontal tumor or abscess or by inflammatory exudate from sinusitis. Lesions of the chiasma itself are most often the result of tumor of the pituitary body which by its position at the *chiasma itself frequently gives rise to a bi*temporal hemianopia and whitened pap illae

Papilledema choked disk often im properly called optic neuritis is the conse quence of a rise of intracranial pressure whereby cerebrospinal fluid is forced down the sheath space of the nerve and appears at the nerve head or papilla This only indi rectly affects the nerve and for a long time is compatible with perfect vision but even tually the fluid becomes organized the nerve fibers are compressed and secondary optic atrophy occurs Primary optic atrophy may come from tabes or from poisoning with methyl alcohol The constant use of the ophthalmoscope is essential in neurologic medicine and almost essential in all branches of medicine This instrument is more indis pensable than a stethoscope.

Slight *irregularity in the shape of the pupils* always suggests that lues may have produced changes in the ciliary ganglion or in the ciliary nerves Changes in the nuclei of the third nerve or in the ciliary ganglia may produce the classic *Argyll Robertson pupil* This is ingravescent by the following stages

1 A pupil contracting sluggishly to light and briskly on convergence

2 One fixed to light and brisk on con vergence

3 One fixed to light and sluggish on con vergence.

4 Fixed to light and fixed on convergence

These phenomena are most often due to lues but may be seen as a result of epidemic encephalitis of acute alcoholism or even of tumor provided that the paths of the pupil reflexes be so slightly involved as to damage one set of fibers and not the other The opposite of an Argyll Roberston pupil *i e*

retention of the power of contraction to light and the loss of that on convergence is characteristic of diphtheritic nervous infection but may also be occasionally due to periaqueductal lesions such as encephalitis

The patient must be made to turn the eyes at different speeds in all directions, to reveal any strabismus loss of ocular movement nystagmus or diplopia *Strabismus* may depend on a long-standing refractive error but if recently acquired is most probably due to paralysis of one of the extrinsic ocular muscles and overaction of the unimpaired antagonist For instance, a lesion of the third nerve may produce paralysis of the pupil ptosis of the lid and eversion of the eyeball from uncontrolled action of the unscathed external rectus muscle supplied by the intact sixth nerve A slight paresis (weakness) of an ocular movement permits light to fall from a seen object on different parts of the two retinae, this produces diplopia or double vision The smaller the muscular error the more distressing the diplopia seems to the patient because with slight failure of parallelism in the eyeballs the sensitive macular region of the retina and the but slightly less sensitive perimacular region are in operation so that the true image is very little more distinct than the false

Loss of *conjugate movement* of the eyeballs may be discovered at this time due to some lesion of the quadrigeminal plate such as a pineal tumor or encephalitis or even a midbrain luetic meningitis This is occasionally seen also in myasthenia gravis *Nystagmus* is an involuntary rhythmic ataxia or incoordination of the eyeballs usually bilateral and more often found on conjugate movement than when the eyeballs are stationary In its true form it depends on a lesion of the cerebellum or its tracts in the pons medulla and midbrain Lesions of these structures give rise to decomposition of rhythmic movements so that motor ataxia of the arms and legs results This so called 'intention tremor of the hands is a manifestation of pure cerebellar disease and is strictly analogous to the nystagmus of the eyeballs, caused by similar structural defects Nystagmus may come from labyrinthine disease through the connections of the vestibular nerve with the cerebellar system by Deiter's nucleus, and it is occasionally present in somewhat different form in high myopes and albinos

The *fifth nerve* has both a motor and sensory division, the former has its nucleus in the midbrain, the latter in the long descending nucleus in the medulla and first two segments of the cervical cord On the course of the sensory division lies the gasserian ganglion, below which passes the motor root Total palsy of the sensory fifth destroys all superficial sensation on the same side of the face including the cornea, but excluding the skin over the jaw angle which is supplied by the great auricular nerve The mucous membranes of the affected side are included in this anesthesia with the exception of the posterior third of the tongue which receives its supply from the glossopharyngeal nerve Taste is affected in that area of the tongue in which sensation is gone The motor branch supplies the muscles of mastication and when it is paralyzed the masseter and temporal muscles atrophy on the affected side, and the lower jaw when opened deviates to the side of the lesion by reason of the inaction of the ipsolateral external pterygoid muscle

If the *seventh nerve* be affected in the pons there is usually also a lesion of the ipsolateral sixth nerve, due to the proximity of the sixth nucleus to the intrapontine seventh nerve Paralysis of the nerve produces motor palsy of the same side of the face and the forehead cannot be wrinkled the eyelid properly closed, nor can the orbicular mouth muscles be used for laughing, whistling, or emotional expression This paralysis renders eating and drinking arduous Liquids are apt to be spilled owing to the difficulty in closing the lips If the chorda tympani be involved as when the lesion is in the fallopian aqueduct, the sense of taste is affected in the anterior two thirds of the same side of the tongue

The *eighth nerve* consists of two sets of fibers having different functions the cochlear branch from the organ of Corti the nerve of hearing and the vestibular branch from Scarpa s ganglion in the vestibular apparatus the nerve ' as it were by which movement and posture are appreciated The cochlear function is examined by a ticking

watch and by seeing if a vibrating tuning fork is better heard by air or bone conduction. In deafness of middle ear origin, the former is lost and the latter retained If the cochlear nerve be destroyed (so called nerve deafness') both conductions are blocked

Tests for the functional integrity of the vestibule consist in syringing the tympanum with hot and cold water to see if nystagmus and vertigo be produced. Rapid rotation of the individual is also often valuable in this determination

The functions of the *remaining three cranial nerves* are examined by making the patient protrude the tongue and by looking carefully for such signs of muscular atrophy therein as tremor of fine fibrillary' character, undue furrowing especially unilateral or deviation from the middle line of the teeth, by examining the movements of the palate on deep inspiration and phonation (the uvula in the presence of unilateral palatal palsy is lifted toward the sound side), by inspecting the vocal cords and determining if an abductor palsy be present due to involvement of the recurrent laryngeal nerve The patient must be made to shrug his shoulders and rotate the head against resistance to discover a possible spinal accessory lesion giving rise to paralysis of the sternomastoid and upper third of the trapezius muscle

The Motor System.—Inspection and palpation reveal loss of power in a muscle or group of muscles, and any changes in tone The movements at each joint should be tested against resistance The patient should extend the hands abduct the arms raise them above the head grasp the observer s hands firmly and show his power for pulling and pushing movements at the elbows With the arms folded across the chest he should try to rise from the bed then all movements at the hip should be executed and appraised in power likewise at the knee and ankle

By palpation it is possible to estimate the nutrition of muscles if it be diminished the muscle is said to be *atrophic* if increased *hypertrophic* Occasionally in certain muscular diseases (so called myopathies) the apparent muscle volume is increased while its power is greatly lessened (pseudohypertrophy)

The *distribution of paralysis or paresis* is determined by the site of the lesion Thus injury to one internal capsule produces hemiplegia or paralysis of the face arm, or leg of the opposite side, injury to say, the pons extensive enough to include both pyramidal tracts produces diplegia or double hemiplegia, a spinal cord injury is apt to cause paralysis of both legs or paraplegia and if it be in the cervical region a tetraplegia in which all four limbs are included

The tone of muscles weakened by a lesion of the corticospinal motor tract (upper neuron palsy) is usually increased (spastic) and decreased (*flaccid*) when the lesion is in the motor system between the anterior horn cells and the motor end plate (lower neuron palsy) The characteristics of these two great types of paralysis may be further tabulated as shown below

Upper Neuron Palsy Supranuclear Type

Movements" are paralyzed rather than single muscles or groups of muscles
Spasticity or increase of muscle tone
No atrophy
Reaction of muscles to electricity normal.
Deep reflexes increased Arm jerks knee and ankle jerks
Plantar reflex of Babinski type extension of great toe on stimulation of the sole of the foot.

Lower Neuron Palsy Nuclear and Infra-nuclear Type

Single muscles or groups of muscles affected if due to spinal lesion in spinal segmental distribution
Flaccidity or decrease of muscle tone
Atrophy the rule.
Electric reactions those "of degeneration " No reactions to faradism and an abnormally slow vermiform contraction to galvanism.
Deep reflexes decreased or lost.
Plantar reflex may be lost, but if present is of flexor type

Tone and posture are influenced also by brain lesions not of the pyramidal or corticospinal system but of the extrapyramidal or striatospinal system This mechanism phylogenetically older than the other dominating instrument controls attitude tonus and automatic associated movements The disease most characteristic of this lesion is paralysis agitans in which attitude or posture of the body and limbs is altered tonus is greatly increased so that the limbs when passively moved convey to the examiner a feeling of cogwheel rigidity automatic associated movements (such as swinging the arms when walking) are decreased or lost,

and tremor superadded by reason of interference with the rubrospinal tracts

It has been stated above that the position of the lesion and the structures it affects determines the type of paralysis produced Many combinations, of course, are possible, and while multiple lesions may occur in the brain and give rise to strange medleys of defective function it is always wise for the beginner to determine shrewdly whether one lesion correctly placed could produce the *existing condition Thus a hemorrhage* in the *crus cerebri* produces paralysis of the contralateral face, arm, and leg and almost certainly by its incidence on the third nerve an ipsolateral ptosis of the eyelid and defective movements of the pupil of that eye and of the superior, inferior and internal rectus muscles If the hemorrhage be large enough to implicate the red nucleus the weakened arm and leg are ataxic and the seat of tremor In similar fashion a unilateral pontine lesion may produce contralateral hemiplegia and ipsolateral palsy of the fifth sixth seventh, and eighth nerves *Bulbar lesions* naturally interfere with the functions of the cranial nerves therein so that there is trouble in swallowing in articulating or in phonation

A lesion for example of the *seventh cervical segment* of the cord produces spinal level signs of lower motor neuron type, with interference with the functions of the seventh segment *e g* paralysis of the intrinsic hand muscles with retention of movements at the shoulder (supplied through the fifth and sixth segments) and pyramidal tract paralysis (upper motor neuron type) below the lesion level, that is to say spastic paraplegia with sensory paralysis below the distribution of the seventh segment diminished arm jerks, and increased deep reflexes in the legs Sphincter paralysis also occurs

A *middorsal lesion* gives rise to spastic paraplegia also the arms are not implicated but owing to the longer innervation of the recti abdominalis muscles from the dorsal cord the upper recti remain intact while the lower are paralyzed The attachment of the umbilicus to the sheath of the rectus muscle determines then in this situation that on attempts to contract the recti muscles (as in rising from the recumbent position) the umbilicus will not remain stationary as it does normally but will be pulled upward 1 or 2 inches by the unantagonized superior recti muscles

A lesion of the *cauda equina* produces a picture determined by the functions of the nerve roots contained in the lowest part of the spinal dura mater sheath The motor loss is of *lower neuron type, characterized* by atrophy of the affected muscle group *with electric reaction of degeneration* and loss of the deep reflexes subserved by the roots affected If the sacral roots be involved there is usually sphincter paralysis and, in any case, if the posterior spinal roots be included in the damaged area there are characteristic shooting root pains Such loss of sensation as may be present is found in the skin areas sensorily served by the affected roots

The paralysis consequent to inflammation or injury of any nerve or plexus of nerves is of course, of lower neuron type, and is confined to the muscles supplied by the affected nerves

Multiple neuritis due to some general constitutional intoxication (alcohol, lead diphtheritic toxin diabetes lack of vitamin B) is a symmetric disease which produces dropped hands and dropped feet and is due to the especial incidence of the poison on *the extensors of the fingers* and hands and the anterior tibial and peroneal muscle groups The palsy is flaccid and atrophic with loss of reflexes and is usually associated with pain *in the affected muscles and loss* of sensation following 'a glove and stocking' distribution due to the failure of function in the terminal twigs of the mixed peripheral nerves

During the examination of the motor system, myopathies must be looked for These are primary muscular diseases which occur in predisposed stocks *The cause is unknown* the peculiar distribution of the muscular weaknesses, the absence of changes in reflexes (other than from mechanical reasons due to extreme muscle atrophy) and of sensory changes combined with the presence of pseudohypertrophy *in certain muscles* especially those of the calves and the infraspinati due to the *fatty changes* in the degenerating muscle, usually give the clue to correct diagnosis.

Ataxia or *incoordination* of the arms is

sought for by asking the patient to bring his fingertips together with the arms extended before him to touch his nose or his ear with each index finger, and to follow with his hands the movements made by the observer's finger The first two tests are carried out with the eyes open and shut Ataxia of gait is tested by asking the patient to walk along a straight line and to stand still with the feet together and the eyes shut This is known as Romberg's test Ataxia may depend on loss of sensation from the affected limb especially on loss of the sense of position, such as occurs typically in disease of the posterior columns like tabes dorsalis The patient is able to guide the limb by the eyes but in the dark or if the eyes be shut he loses' the limb does not know exactly its position and brings it, smoothly enough to the wrong place. This form of ataxia thus arises *from a purely* sensory defect whereby inadequate information is received

The other great class of ataxias is entirely motor in origin and is due to a defect in the cerebellum or its tracts The function roughly speaking of this organ is to compose to make smooth cortical impulses When this function has been impaired the movement of the limb is broken up into its component parts and becomes jerky The patient is always aware of the position of the limb in space but he lacks the controlling mechanism to bring it smoothly and with properly graduated forces to its objective This *failure to synchronize* muscular action is known as asynergia and results not only in the jerky movements described but in dysmetria which consists in overshooting the objective because of failure to control nicely the strength required for the task. Dysmetria may occur though with a different aspect in ataxia of sensory origin In this the *spatial relationship* between the limb and the objective is poorly estimated and the wrong movement is well performed

The gait of a 'sensory ataxic is stamping in character The tabetic is constantly in the position of a normal person who on going up a flight of stairs in the dark thinks there are eight steps when there are but seven He miscalculates the distance between his foot and the ground in a way the tabetic does all the time A cerebellar gait is more reeling or drunken." If only one cerebellar lobe be affected the ataxia is on the same side as the lesion, and the patient tends to fall to that side This ipsolaterality of cerebellar ataxia depends on the fact that each cerebellar lobe controls impulses coming from the opposite cerebrum which in turn sends impulses to the opposite side of the body through the decussation of the pyramids

Under the heading *involuntary movements* are classified chorea the jerky non purposive character of which has a definite cerebellar quality athetosis, slow vermiform movements which occur in a hemiplegic limb in the producing lesion of which a thalamic component has occurred, fibrillary twitching fine rippling movements of parts of the muscular bellies which occur typically in amyotrophic lateral sclerosis but which are indicative of all acute degeneration and impending or progressive muscle atrophy myoclonus in which an entire muscle or muscle group is twitched often rhythmically and violently seen in both acute and chronic epidemic encephalitis as a release phenomenon from the basal ganglia of the same general pathologic pattern as athetosis and tremors fine such as are seen in exophthalmic goiter or coarse from lesions of the tegmentum of the pons or crus with changes in the rubrospinal tracts

Reflexes—The reflexes are divided into the superficial the deep and the 'organic types

Superficial Reflexes—In the first group the corneal has already been considered The *pharyngeal* and *palatal reflexes* consist of contraction of the pharynx and elevation of the palate when either is touched and depend for their production on integrity of the glossopharyngeal nerve and the bulb They *may be entirely absent in hysteria and in* the absence of organic disease

The *abdominal reflexes* are obtained by stroking with some hard instrument (a pencil or key) parallel with the ribs and also with the inguinal folds Their spinal level runs from the eighth to the twelfth dorsal segments They are very rarely absent in healthy young or middle aged persons whose abdominal walls are not obese If bilaterally absent in young persons a suspicion of early

multiple sclerosis may be entertained In *cerebral hemiplegia* the abdominal wall (transversalis rectus abdominis, and internal oblique muscle) usually does not contract on stimulation of the paralyzed side, and reduction of the force of this reflex on one side is often early intimation of a slight or ingravescent lesion of the motor tract supplying that side Efforts should be made to see whether the abdominal reflexes on one or both sides are fatigable, repeat stimulation if necessary for five minutes Recently this procedure indicated to the writer the correct side of a brain tumor in a child

The *cremasteric reflex* elevation of the testicle on stroking the inner side of the thigh is less dependable than the abdominal reflex It may be retained in the presence of a complete hemiplegia, but is more probably reduced or lost Its segmental level is the first and second lumbar

The most important superficial reflex is the *plantar* To evoke this the blunt instrument is stroked with some force along the outer side of the sole from behind forward Normally this is followed by a flexor movement of the great toe and a contraction of the tensor fasciae femoris Care must be taken not to overstimulate as this produces a defensive withdrawal and dorsiflexion of the foot If the motor tract or the leg center in the cortex be injured, this normal flexor type of plantar reflex is replaced by a slow extensor movement of the great toe, a fanning' spread of the other toes, and a contraction of the hamstring muscles This extensor reflex is the so called Babinski sign' It is always pathologic, being a more primitive type of spinal reflex than the flexor response and is normally controlled by the cortex It is physiologically present in infants unable to walk It may occur for a few minutes to an hour after an epileptic convulsion sufficiently severe temporarily to exhaust the cortex

The writer has observed that the first indication of a pyramidal tract having come as it were under fire is a change in the posture of the affected leg and foot when the patient is lying relaxed in bed There occurs an eversion of the leg and foot in contrast with the other limb The position resembles or approaches that occasioned by a fracture of the neck of the femur This sign is valuable and delicate and most often can be found before the development of Babinski's reflex It might be called pyramidal eversion of the leg and foot.

The *bulbocavernosum reflex* is elicited by placing the finger on the urethra behind the scrotum and at the same time stimulating by pin prick the glans, normally the urethra is felt to contract sharply This phenomenon is lost early in tabes dorsalis and is abolished by any lesion of the caudal roots of the third and fourth sacral segments

The Deep Reflexes—The *biceps triceps* and *supinator jerks* depend on the integrity of the reflex arc through the fifth cervical to the first dorsal segment. They are obtained by tapping the biceps tendon the styloid process of the radius and the triceps tendon

The *knee* and *ankle jerks* obtained by tapping the patellar and Achilles tendons when the supporting muscles are entirely relaxed, have segmental levels of third and fourth lumbar and first and second sacral respectively If feeble they can be increased by making the patient lock his hands together and pull one against the other They are abolished by any break in the arc, by multiple neuritis where the break occurs low down in the peripheral nerves, by tabes dorsalis, Friedreich's ataxia or subacute combined sclerosis of the cord, the lesion here being in the posterior roots or columns of the cord by disease of the motor anterior horn cells of the cord as in acute poliomyelitis and amyotrophic lateral sclerosis, or occasionally by cavity formation in the cord (syringomyelia) As has been said, myopathies may abolish the reflexes by destroying the muscular mechanism needed for their production These reflexes are exaggerated in the presence of pyramidal tract disease in which case the normal cortical control of the cord is withdrawn so that the cord is allowed independent action.

Increased deep reflexes unless unilateral are not so valuable a sign of organic disease as is their loss When these reflexes are increased one must look for *ankle clonus* a rhythmic contraction of the soleus muscle obtained by continued passive stretching of the Achilles tendon *The organic motor reflexes* depend on the vegetative nervous sys

tem and cause contraction for the most part of nonstriated involuntary muscles The most important are the ciliospinal whereby the pupil dilates on scratching the skin of the neck and the oculocardiac whereby the heart is slowed some ten beats a minute by compression of the eyeballs in their sockets This is especially marked in vagotonic persons and may be abolished in tabes

later by the establishment of a reflex automatic bladder action whereby the bladder content is discharged periodically by the production of a primitive mass reflex in response to stimulation of the sole or the inner side of the thigh

Sensation—It would be well here to recollect in outline the paths in the central nervous system of the various forms of sen

Fig 183—Chief sensory pathways ascending from the spinal cord (Villiger s Anatomy of the Nervous System)

The reflex centers of the vesical rectal uterine and genital automatic actions are in the lumbar and sacral segments of the cord and also in the hypogastric and hemorrhoidal plexuses of the vegetative nervous system. Periodic reflex bladder incontinence is normal in infancy after total transverse spinal cord lesion there is an initial period of urinary retention followed in a week or two by overflow dribbling and a week or two

sation These pass upward from the periphery to the posterior roots of the cord thence they pass into the cord and are distributed as follows the fibers bringing sensation from the muscles and joints together with a few of those for touch pass upward uncrossed in posterior columns to the gracile and cuneate nuclei on the same side of the medulla as they entered the cord Thence they continue upward and cross the middle line in the

internal arcuate fibers forming the sensory decussation of the fillet The fibers continue through the crus cerebri to the optic thalamus, where redistribution again takes place some ending in the thalamus, others continuing to the rolandic area of the cortex

The remainder of the tactile fibers and those conveying temperature and superficial

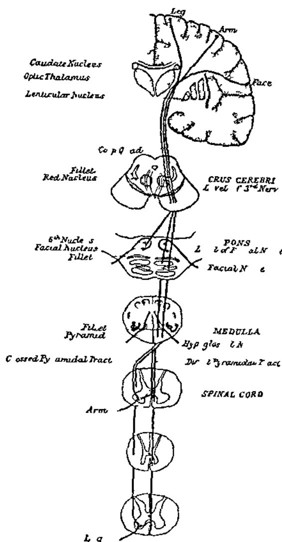


Fig 184—Diagram of the pyramidal tract (the chief motor pathway of the nervous system) (Purves-Stewart s Diagnosis of Nervous Diseases)

pain sensations entering by the posterior roots cross the spinal cord almost immediately and go up the opposite side of the cord from which they entered in the spino thalamic tract of the lateral column When they reach the thalamus the same redistribution takes place, as has been mentioned Some impulses pass on to the discriminating centers of the postrolandic and supramarginal gyri others end in the nuclei of the thalamus, which in this manner is a terminus for various types of undiscriminating sensation of an emotional character (pleasure pain, and some visceral sensations)

To recapitulate, the sensations of deep pressure pain (such as that produced by squeezing the calf muscles) of vibration (ability to appreciate the vibration of a tuning fork placed on bone), of sense of position of joints (whether they be flexed or extended) and some touch sensations ascend the same side of the cord as they enter on to relay stations in the posterior column nuclei in the medulla From there they cross to the opposite side in the fillet to the optic thalamus, and either end or are relayed to the sensory cortex

Sensations of temperature (distinguishing between hot and cold), of superficial pain (pin prick), and the majority of superficial touch sensations enter the cord as do the others by the posterior roots cross the cord immediately and ascend to the thalamus in the lateral ground bundle or lateral column, where they are dealt with as already described

These sensations do not reach the cortex as pain temperature touch etc, at this highest level judgment and selection of sensation occurs whereby spatial relations and differentiation of objects (stereognosis) and discrimination of intensity take place

It is well here to set down, if only as a method of remembering the functional anatomy of the cord the symptom complex known as *Brown Sequard s paralysis* produced by a lesion destroying one lateral half of the cord On the side of the lesion from section of the descending pyramidal tract there will be upper motor neuron paralysis of the leg with increased deep reflexes and an extensor type of plantar reflex From section of the posterior columns and interruption of the uncrossed fibers from the posterior roots below the lesion there results on the side of the lesion loss of sense of position of the limb loss of vibration sense and loss of deep pressure pain sensations At the level of the lesion there is an ipsolateral zone of loss of touch temperature and superficial pain due to interruption of the local fibers of the posterior roots

On the body opposite to and below the

lesion there is loss of sensation for temperature and superficial pain and some depression of touch appreciation due to the cutting of the spinally crossed fibers for these functions coming from the opposite side of the cord. There will be no motor paralysis on this side

The beginner would do well to avoid complicated instruments for sensory examination a pin a wisp of cotton a tuning fork and two test tubes of hot and cold water

The examination of the trophic functions or as they are still called the trophoneuroses' is best understood from the chapter on those conditions The same is true of the examination of the cerebrospinal fluid, of aphasia and convulsions The vegetative nervous system is dealt with, as far as our clinical knowledge of its functions is concerned in the section on endocrinologic conditions.

FOSTER KENNEDY

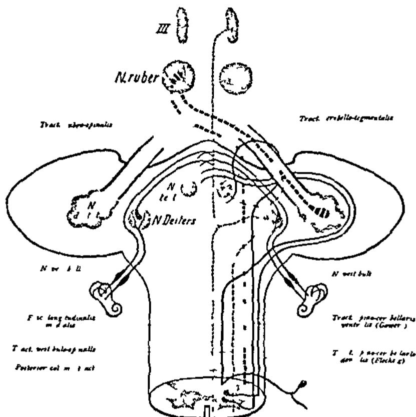


Fig 18.—Important pathways to and from the cerebellum (Villiger's Anatomy of the Nervous System)

added to intelligence and patience are adequate equipment Knowledge of the types of sensory loss must be added to this armament the skin areas served by the plexuses and the peripheral nerves the spinal root areas and familiarity with the phenomenon of dissociated sensation which has just been described as occurring in Brown Sequard palsy and is also seen in syringomyelia (central lesion of the cord involving pain and temperature fibers at the point of their spinal decussation but sparing the other sensory fibers less centrally placed)

REFERENCE

Aids to Investigation of Peripheral Nerve Injury" M R C War Memo No 7 H M Stationers Office, 1942

THE DIAGNOSTIC SIGNIFICANCE OF THE CEREBROSPINAL FLUID

History.—The study of the cerebrospinal fluid which now embraces physical histologic chemical bacteriologic biologic and immunologic methods had its beginnings in 1891 when Quincke demonstrated the

method of lumbar puncture The first punctures were performed for therapeutic purposes, to reduce pressure in hydrocephalus and in tuberculous meningitis Soon afterward fluid was also withdrawn in acute meningitis

Following closely on the diagnostic and therapeutic application of lumbar puncture in meningitis, the procedure was employed on patients with syphilis of the nervous system so that the fluid might be examined But in the first decade of this century the only criteria of value were the cell count, differential cell picture and globulin reaction In this pioneer work the French workers Ravaut Sicard, and others led the way In 1910 Mestrezat published his epoch making book which emphasized the chemical aspect and laid the foundation for much subsequent work At this time the Wassermann reaction took its place with chemistry, cytology, and bacteriology and the diagnosis of neurosyphilis became clarified by the demonstration of the 'four reactions of Nonne' namely a lymphocytosis, an increase in the globulin content and a positive Wassermann reaction in the blood and in the spinal fluid

Colloidal chemistry entered the field in 1913 with the publication of Lange s gold chloride test The gold sol test attracted immediate attention and as it now seems, assumed unwarranted importance it certainly led to neglect of the previously known fundamental tests

Little attention had been paid to pressure although Quincke in his original work used a manometer Since Queckenstedt s article on hydrodynamic tests appeared in 1916 however, pressure studies at the bedside have been added to the tests carried out in the laboratory

Later attention was called to 'fractional examinations of the spinal fluid that is, examination of the first and last portions of fluid obtained on lumbar puncture This method was designed to give evidence of the chief locus of pathology whether cerebral spinal or diffuse This method was promptly superseded by methods of multiple punctures cisternal, ventricular and even puncture of the thoracic and cervical subarachnoid space

The present advance in our knowledge of the cerebrospinal fluid as indication of disease appears to be *largely in* the field of chemistry, with close correlation of blood and fluid by means of *micro chemical tests*

Anatomy and Physiology —The cerebrospinal fluid is found in the ventricles of the brain the subarachnoid spaces of the brain and spinal cord and, according to some observers in the perivascular spaces The normal amount is approximately 150 cc, under abnormal physiologic and pathologic states this amount may be very considerably increased While the whole fluid system is intercommunicable the fact that the composition of the ventricular fluid differs considerably from that of the subarachnoid space is evidence that admixture is not prompt or complete

According to Weed, there appears to be a dual source of the fluid although whether it is a secretion a filtrate or a dialysate is not certain Most of the fluid appears to come from the choroid plexus of the lateral ventricles whence it passes through the third ventricle and aqueduct of Sylvius into the fourth ventricle and then by way of the foramina of Magendie and Luschka into the cisterna magna to mix with a smaller amount of fluid which seeps into the cerebral subarachnoid space by way of the perivascular spaces The exact point of *origin* of this latter fluid is in doubt From the cisterna magna which Dandy *describes* as the distributing center the cerebrospinal fluid passes forward along the *base of* the brain and upward over *the convexities* where it is absorbed into the venous sinuses by means of the arachnoid villi *There* is also a downward course into the spinal subarachnoid space whence it is in *part* absorbed by the arachnoid projections which cover the spinal nerves

Movement of the *fluid* must not be thought of as a stream or a flow but as admixture and diffusion *affected* by variations of pressure caused by pulse, respiration etc Normally slow *movements* of fluid from one *locus to another* may be *rendered* quite rapid under artificial conditions of pressure and drainage *although* they are always more rapid when in the direction of the normal trend

Only one function of the cerebrospinal fluid is known the mechanical protection of

the brain and spinal cord That it also serves metabolic functions is likely, but what these are and how they are performed is not known

Loci at Which the Cerebrospinal Fluid May Be Obtained—Long before fluid was obtained by design occasional opportunities were offered for its examination in cases of rhinorrhea following fracture of the cribriform plate This accident is rare and examination of the fluid of little value except as it indicates the large potential output (approximately 1 liter a day) Since 1891 fluid has been obtained for diagnosis primarily by lumbar puncture The needle enters the caudal end of the subarachnoid space below the conus which lies opposite the first lumbar vertebra in this space occupied only by the roots of cauda equina nerves cannot be injured for it is impossible to prick a nerve floating in fluid There are five interspaces at which lumbar puncture may safely be made the most convenient of which may be used in any given case Other places at which cerebrospinal fluid may be obtained should be mentioned The lateral ventricles are accessible in babies through the open anterior fontanel and in adults through trephine openings the cisterna magna is readily reached by suboccipital puncture by the experienced operator and puncture of the *cervical and thoracic subarachnoid* space rarely indicated, is quite possible Cisternal puncture has been advocated as a substitute for lumbar puncture to avoid postpuncture headache a point of view with which the writer is not in sympathy

Tests—Among the many tests which have been recommended in studying the cerebrospinal fluid a few stand out as of proved value With 10 cc of fluid or even less all of the most important may be performed and fortunately several of the most *significant* can be *carried out literally at the* bedside. A number of special examinations are also of value in certain investigations but it is the writer's opinion that the results of the following group of tests when carefully analyzed and correlated with the clinical findings give reliable and valuable information

Physical Characteristics—The fluid which is normally crystal clear may be turbid from bacteria or cells or actually purulent The formation of a clot on standing indicates that fibrin is present and is always pathologic Purulent fluid may be yellow green white, or muddy, according to the bacteria *present A clear yellow coloration is pro*duced by pigment from the blood and may indicate antecedent hemorrhage or venous stasis characteristically due to compression *of the spinal cord* Whether disease or technic is responsible for blood tinged or bloody fluid must be determined at the time of puncture If it is due to faulty technic the blood will rapidly diminish in amount as fluid is withdrawn, as shown in successive tubes This method of fractional examination' especially useful in determining the site of bleeding can be used for other purposes for occasionally more cells or greater protein are found in the last tube of fluid taken than in the first suggesting that a focus of pathology has been opened up by withdrawal of fluid

Pressure and Dynamic Studies—Normal pressure with the patient in the lateral position and completely relaxed is usually between 100 and 150 mm in the aqueous manometer For clinical purposes this may be measured with sufficient accuracy by allowing the fluid to run into a glass tube with a 2 mm bore A pressure above 200 mm is suspiciously high and above 300 mm almost *always denotes increased intracranial pres*sure The significance of low pressures is less certain The manometer demonstrates pulse oscillations and respiratory excursions the former usually 1 to 2 mm the latter 4 to 6 mm in extent

With the manometer in place and oscillations visible an assistant presses gently on each side of the larynx separately and then together until the carotid pulse is palpable By this maneuver which compresses the jugular veins venous stasis is immedi*ately produced in the* cranium this results in increased intracranial pressure which under normal conditions is transmitted promptly throughout the cerebrospinal fluid and is registered by a marked and prompt rise in the lumbar manometer This test is useful in the diagnosis of a number of conditions leading to spinal subarachnoid block tumors of the cerebellar fossa and lateral sinus thrombosis Rarely a drop in pressure occurs while carrying out this test and it

will be found that an irritable carotid sinus has been stimulated

Cytology—One of the earliest tests employed and still one of the most important *examinations* is that of the cell content of the fluid Normally no cells are present, or only a rare arachnoid cell Some observers maintain that as many as ten lymphocytes per cubic centimeter of fluid is normal but the writer thinks that the presence of ten lymphocytes or even five is pathologic and requires explanation

A count of more than ten lymphocytes is almost universally admitted to be pathologic, and to be evidence of an inflammatory process somewhere within the cerebral or spinal subarachnoid spaces A certain differential value is attributable to high and low counts as will appear in later sections *The count should be carefully obtained from* well mixed freshly drawn fluid in the regular blood counting chamber under the high power objective This permits identification of the cells

Differential counting of cells is simple in acute exudative fluids by means of ordinary stained films but in fluids containing few cells it is difficult because the cells are readily lost in the process of making the film and often stain poorly on account of distortion due to prolonged immersion in the fluid At least three types of cells should however be recognized even in the counting chamber—the lymphocyte, the polymorphonuclear leukocyte and the large arachnoid mononuclear cell With special care, plasma cells and eosinophils may be identified and tumor cells have occasionally been reported present. The significance of cell types as well as of cell numbers is obviously great Tumor cells from meningeal emplacement have rarely been reported as also large cell counts in leukemia

Chemistry—PROTEIN DETERMINATION in the cerebrospinal fluid is of fundamental importance Normally very slight (20–40 mg *per* 100 cc.), the protein content may increase pathologically (up to 4 Gm per 100 cc) until it approaches that of blood serum This must be looked upon as a non specific reaction of exudative or transudative origin Rough examination with the naked eye is of value when once the examiner has learned the normal turbidity The nitric acid trichloracetic acid and other tests demonstrate the presence of coagulable protein but perhaps the most simple of all is the mixture of three parts of 95 per cent alcohol with one part of spinal fluid These tests normally produce a faint protein flocculation easily recognizable from gross pathologic amounts So great is the importance of even a slight protein increase that a quantitative estimation is desirable, for this purpose the sulfosalicylic acid method of Denis is recommended

Unquestionably, *quantitative estimation of the globulin and albumin contents* separately will be of value when reliable micro *chemical tests have been perfected* At the present time the globulin ring test of Ross Jones (saturated solution of ammonium sulfate underlying an equal amount of spinal *fluid) gives* a rough *index of the amount of* globulin present Normally no cloud is seen at the junction of fluid and reagent but in neurosyphilis in particular a well defined cloud indicates a marked globulin increase even when the total protein content (*i e* albumins and globulins) shows no great increase by the sulfosalicylic acid method

SUGAR—Normally the lumbar fluid contains about 0 065 per cent sugar It is now well determined that a diminution or even a loss of sugar occurs regularly in acute meningitis and tuberculous meningitis High sugar content usually reflects a high blood sugar reading, under experimental conditions an intravenous injection of glucose is reflected in the cerebrospinal fluid in about two hours Quantitative tests for sugar when these diseases must be considered in *diagnosis* are therefore necessary A rough macroscopic method is here of little value although failure of Benedict s solution to *reduce* with three drops of fluid suggests a diminution in the sugar content

CHLORIDES—The chloride content is regularly low in bacterial meningitis

NONPROTEIN NITROGEN UREA URIC ACID AND CREATININE.—Tests for nonprotein nitrogen urea uric *acid and creatinine are* occasionally made for example in uremia but are not recommended as of routine value

COLLOIDAL TESTS—Three colloidal tests have been widely recommended the original test of Lange using *gold chloride* the gum

mastic test of Emanuel and the *benzoin test* of Guillain

The mechanism of precipitation by these tests is not understood but certain changes occur with different dilutions of spinal fluid which are more or less characteristic of a number of diseases The earlier workers unquestionably assigned to these tests particularly the gold sol test altogether too much value One type of curve in the gold sol test has however retained its importance the misnamed paretic curve now usually spoken of as first zone reaction This type of reaction represented by discoloration of the gold chloride reagent by the stronger dilutions of spinal fluid and by complete precipitation of the benzoin and mastic test reagents is certainly characteristic of paresis although it is not pathognomonic Like others colloidal tests have a distinct place in the complete analysis of the spinal fluid Alone they are of little value

Biologic Test —This is the Wassermann test.

Bacteriologic Tests —These are the same as in the study of other fluids and exudates by means of films and cultures Guinea pig inoculations for tuberculosis rabbit inoculations for *Treponema pallidum* the monkey inoculations for poliomyelitis must be considered as exceptional or research procedures and not applicable to routine examination of the fluid The use of *dyes* to demonstrate permeabilities *air* and *opaque substances* for the purpose of x ray localization are obviously not the part of a routine examination of the fluid Nor is the use of drugs designed to test permeability of the encephalic barrier upon a sound routine basis

Summary.—When diagnosis is doubtful and the spinal fluid is to be examined the routine procedure should be to perform lumbar puncture with the patient in a lateral horizontal position take the initial pressure reading with an aqueous manometer observe the increase of pressure during compression of the jugular veins separately and combined and the rapidity and degree of fall after release of the jugular veins and observe the pressure after withdrawal of 10 cc of the spinal fluid so that the difference between the initial and final readings may give some indication of the total quantity of fluid in the cerebrospinal spaces In the laboratory the cell count and differential cell count should be determined the protein content ascertained by the quantitative method if possible the globulin ring colloidal (preferably gold sol or benzoin) and Wassermann tests made, and the sugar content determined quantitatively if the fluid has not stood too long Bacteriologic studies are desirable if there is turbidity or if meningeal infection is strongly suspected

Clinical Application of Tests.—Let us now consider the diseases and pathologic conditions which evoke positive changes in the spinal fluid Because of striking similarity in fluid pathology these may most easily be compared in groups irrespective of their etiology This method also emphasizes any contrasts within a given group

The Acute Meningitides.—By the time that *acute meningitis* is suspected clinically the spinal fluid has usually undergone characteristic changes *i e* increase in pressure increase in the number of cells (polymorphonuclear leukocytes predominating) increase in the protein content and invasion by the infecting organism demonstrable both on film and culture The fluid at first merely cloudy rapidly becomes more turbid and purulent contains increasing numbers of organisms and cells and an increasing quantity of protein and fibrin either preformed or forming in the test tube. Sugar estimation is of great significance in all forms of acute meningitis Sugar is reduced early and rapidly falls a condition unknown in other diseases It should be emphasized that this test must be performed immediately after aspiration of the fluid because the sugar disappears *in vitro*

While the infecting organism is usually found with ease particularly the pneumococcus and streptococcus the meningococcus and *H influenzae* frequently cannot be recovered in the early stages of the disease even in the centrifugalized sediment. In such cases a number of procedures are recommended the spinal canal may be drained to permit recovery of the organism in the last portion of the fluid the neck may be rotated to loosen the exudate which tends to accumulate about the foramen magnum puncture of the cisterna magna may be employed and finally puncture of a lateral

ventricle All of these methods have been employed successfully for recovering the organism and for administering serum

In acute meningitis which has entered into a *subacute stage* there is a tendency for mucofibrinous masses to accumulate in different loci of the spinal and cerebral subarachnoid spaces especially in the lumbar sac and in the upper cervical canal Under such conditions the fluid is thick purulent, and scanty The organisms may be numerous or absent In such instances of meningitic block puncture at a higher level frequently yields plenty of fluid and organisms

Since the introduction of sulfonamides in the treatment of meningitis less frequent examination of the spinal fluid is indicated A preliminary examination however is necessary to determine the type of organism and in cases not doing well puncture at different loci is still indicated to determine the presence of exudative loculation The determination of sulfa drug level in the fluid may be advantageous but as it follows the blood level so closely it is usually not necessary

Numerous organisms attack the meninges but by far the most common are the streptococcus pneumococcus and meningococcus In epidemics the last assumes first place in frequency Other bacteria less frequently recovered are *Staphylococcus aureus* and *albus Bacillus pyocyaneus Hemophilus influenzae B typhosus B coli* and *Micrococcus catarrhalis* *As a rule the meningitis* caused by these less frequent organisms is of a less severe type but variations in the virulence of different strains make such a statement of only general significance

Aseptic Meningitis —Under certain conditions *aseptic meningitis* develops The fluid is usually turbid but colorless and not purulent although showing a polymorphonuclear cytology Most important is the absence of organisms and a normal sugar titer Aseptic meningitis develops in certain fevers such as pneumonia and is thought to result from the action of a toxin which passes into the cerebrospinal spaces A sterile cloudy fluid with 1000 or more cells is frequently seen in aural infections and usually signifies an epidural or subdural abscess It occurs regularly after injection of foreign substances into the subarachnoid space and is therefore a sequela of intraspinal injection of serum Lipiodol used for radiographic localization of tumors of the spinal cord causes a well marked transitory aseptic meningitis with symptoms of meningeal irritation as does air used for the same purpose and novocain injected for anesthetization Even salt solutions, not properly balanced, cause a reaction which may be classified as aseptic meningitis Severe meningeal and myelitic reactions have been caused by injection of various antiseptics

Tuberculous meningitis as a rule runs a fairly definite clinical course likewise the spinal fluid findings vary little with different patients The first fluid examination made early in the illness is usually characteristic of the disease, even though the clinical picture be doubtful, if not at first a comparison of fluid changes on successive punctures in the next few days yields findings which are almost conclusive

Early in the illness the fluid will be found abnormal pressure moderately elevated (200–300 mm) fluid clear or very slightly turbid a clot forming after standing If a sample of fluid is placed on ice a veil like clot appears suspended from the surface (so called pellicle) There will be numerous cells 50 to 100, both polynuclears and mononuclears in about equal proportion protein is markedly increased twice or three times normal Most significant of all the *sugar content is already low* As the disease progresses *the fluid* becomes more and more turbid the cells increase in number the protein also increases but the sugar diminishes

Tubercle bacilli may be found at any stage best obtained by staining the clot but without the bacterial evidence the progressive changes noted in the fluid are highly characteristic Guinea pig inoculation will seldom fail to give positive results but the long incubation period robs this method of diagnostic importance

Acute poliomyelitis acute encephalitis brain abscess and acute lymphocytic meningitis yield fluids which are similar Examination of the fluid alone does not differentiate these diseases and even a succession of examinations over a period of many *days often* fails to do so All have the following in common the pressure is high normal or moderately elevated dynamic tests *normal* the fluid clear or very slightly turbid but color

less The cell count in all is slightly elevated but more frequently less than 100 even the differential cell count is not fixed for while a mononuclear formula is the rule a few to many polynuclears are often present In epidemic encephalitis however polynuclears are rare and in poliomyelitis they are seldom seen after the first day or two of illness The protein tests show slight increase in all and in all the sugar remains normal throughout the illness. Colloidal tests are abnormal but variable in type and not helpful the Wassermann negative

Syphilis of the Central Nervous System — Since the fluid varies with the type of neurosyphilis and the stage and activity of the pathologic process it is necessary to consider separately the typical changes of the different clinical types of this protean disease in order to obtain a clean cut conception

Late Primary and Secondary Syphilis —In late primary and secondary syphilis the fluid frequently contains a moderately increased number of lymphocytes (20–50) a slightly increased quantity of protein and reacts positively to the Wassermann test Since it occurs in so many patients during the efflorescent stage most of whom never develop neurosyphilis it is likely that the reaction often represents an aseptic meningitis comparable with that described above. Still some of the patients presenting this picture early continue to show positive fluid findings and do develop neurosyphilis so that it is reasonable to consider these findings as consistent with incipient syphilis of the nervous system

Acute Meningitic Syphilis —During the first year usually about six months after infection acute meningitic symptoms may occasionally supervene The condition of the fluid in such acute syphilitic meningitis is quite characteristic the pressure is increased (250–350 mm) the cell count is high (500–1000 cells) lymphocytes predominate and polymorphonuclear leukocytes are numerous, the Wassermann reaction is strongly positive and collodal tests are positive but variable in type Fluid taken from patients with this acute meningitis has been shown when inoculated into the testicle of a rabbit to contain the *Treponema pallidum*.

Late Neurosyphilis Active Stage.—While late neurosyphilis may be separated into the tabetic meningovascular and general paretic types clinically it is impossible to do this by examination of the cerebrospinal fluid although one specimen may show a strong and another a weak syphilitic reaction (see Table 1) The strong reaction is found almost without fail in general paresis but is not pathognomonic in that it occurs frequently in less severe manifestations of neurosyphilis Both series of tests unmistakably denote active neurosyphilis but correlation with clinical experience suggests that the stronger reactions indicate more resistant infection and are associated with severe parenchymatous involvement Such reactions are characteristic of general paresis and in this disease are so constantly strong that in their absence a diagnosis of general paresis is questionable Strongly positive reactions may also occur in fluid from patients with tabes and syphilitic optic atrophy The weaker tests are characteristic of tabes and meningovascular syphilis when the process is active and advancing In by far the larger number of progressive cases of late neurosyphilis the reactions are of this character

Late Neurosyphilis. Inactive Stage —Many patients with obvious signs of neurosyphilis will be found to have normal or nearly normal spinal fluid There may be a slight increase in the protein content and a

Table I.—Two Types of Fluid Characteristic of Late Active Neurosyphilis

	Strong" reaction	"Weak" reaction
Cytology	10 to 40 mononuclears Plasma cells present.	20 to 80 mononuclears Plasma cells rare or absent
Total protein	80 to 125 mg per 100 cc	50 to 100 mg per 100 cc.
Globulin ring test	Strongly positive	Weakly positive.
Gold-sol	5 54321000	1123321000
Colloidal benzoin	Strong	Weak
Wassermann	Strongly positive.	Weak, moderate, or strongly positive.
Blood Wassermann	Strongly positive.	Positive or negative

weak gold sol reaction but not increase in the cell count and a negative Wassermann reaction Such conditions are characteristic of an inactive stage of the disease and usually indicate that the process is stationary whatever the extent of degeneration It is however well known that normal or relatively normal spinal fluid may be obtained in clinically active neurosyphilis as is proved by obtaining abnormal fluid from another locus or as evidenced postmortem

Under successful antisyphilitic therapy a return of the fluid reactions to normal is to be expected a drop in the cell count usually being the first sign of improvement and followed by reduction of protein content and a change in the Wassermann reaction The pathologic gold sol curve is often the most resistant abnormality The fluid frequently does not become completely normal even in patients who show persistent clinical improvement Under treatment the fluids of some patients remain fixed" and sometimes react more strongly than before treatment Experience shows that irrespective of apparent clinical improvement such unaltered reactions indicate progress of the disease and therefore a poor prognosis The relation between the clinical and serologic course of neurosyphilis is still debatable and cannot be further considered here

Spinal Subarachnoid Block—Normally the spinal subarachnoid space contains fluid which is freely interchangeable within the spinal canal and subject throughout its length to variations in pressure If at any point this space is constricted two independent fluid chambers are formed Change of pressure on one side of this block is not therefore transmitted to the other side (hydrodynamic evidence of block) and the composition of the fluid below the block also changes The most conspicuous alteration is a marked increase in the protein content presumably due to venous transudation (hydrostatic evidence of block) The most satisfactory although not the only method of demonstrating the hydrodynamic evidence of block is the artificial elevation of intracranial pressure by compression of the internal jugular veins of the neck Normally the pressure rises promptly in the lumbar manometer if block be present anywhere above the point of puncture however, no elevation of pressure occurs The hydrostatic evidence of block is *readily* seen in the marked increase in *protein content* which below the block sometimes approaches that of blood serum

Two *types of fluid* have been described as characteristic of block the *one yellow* which clots on standing (Froin syndrome of *coagulation massive et de xanthochromie*) the other clear and colorless which contains excess protein (Nonne syndrome) Neither type of fluid contains cells except in unusual cases when the block is associated with meningeal inflammation It is quite probable that both represent different degrees of the same process With both types of fluid block may be demonstrated by hydrodynamic tests

Spinal subarachnoid block is caused by a considerable number of pathologic processes which may be classified according to location (1) affections of the spine tumors abscesses pyogenic and tuberculous dislocations (2) intraspinal but extradural epidural abscess tumors (3) subdural tumors of the meninges acute fibrinopurulent exudate chronic adhesions cysts (4) intramedullary tumors gumma syringomyelia rarely

COMPLETE BLOCK—Experience shows that for the most part yellow fluids containing a large amount of protein and showing evidence of block (the Froin syndrome) occur especially in patients with pronounced transverse myelitic symptoms in whom the level of block is well determined by clinical examination

INCOMPLETE BLOCK—There are however numerous patients from whom a colorless fluid is obtained in which there is only moderate increase in protein content and no increase of the cell count (the cyto albuminous dissociation of the French) In them a *partial block* may be demonstrated in a number of ways by a slow rise in the manometric pressure following jugular compression by the existence of a latent period before the rise following jugular compression and by maintenance of a high pressure below the block after jugular release or most commonly by a combination of these three methods In such patients the diagnosis of block is less certain Combined cisternal and lumbar puncture is advisable to permit comparison of the fluids above and below the

block which provides much more conclusive hydrostatic and hydrodynamic evidence than lumbar puncture alone. These tests of the permeability of the spinal subarachnoid space have been of very great service in the early differentiation of obstructive and compressive lesions of the spinal cord from spinal cord affections which are primarily degenerative and do not produce block

The location of a spinal block may be visualized by the use of *iodized oil* In this country lipiodol (Lafay) as advocated by Sicard and Forestier is chiefly used Two cc of oil injected into the cisterna magna will fall when the patient is sitting to the top of spinal block and can there be seen by x ray film or fluoroscope If injected by the lumbar route and the patient placed in the Trendelenburg position the oil may be seen to stop at the lower pole of the blocked area The experienced observer may obtain from the character of the shadow not only help as to localization but also as to etiology

Cauda Equina Lesions—Tumors of the cauda equina not infrequently will give fluids similar to those of cord tumors just described with subarachnoid block and greatly increased protein as the significant findings *provided that lumbar puncture is made below the tumor* But as this is often difficult or impossible we must rely upon what evidence is obtained from puncture directly above the tumor and here we find a high protein fluid which is frequently yellow The further above the tumor the less abnormal is the fluid a fact readily demonstrated by multiple punctures The fluid above a cauda tumor is therefore similar to that from below but always less abnormal and most significant of all shows *no evidence of block*

Occasionally soft vascular tumors fill the lumbosacral canal as evidenced by persistently bloody fluid on puncture In such a case we must be on guard to distinguish between blood obtained from a tumor and bloody fluid from faulty technic (see later)

Of all the causes of low back pain and sciatica *herniation of an intervertebral disk* —usually L 4/5—has been found a frequent cause The majority of such herniations are accompanied by slight or moderate increase in the protein content of the fluid The fluid in most other conditions causing the same symptoms is normal except in cauda tumor in which case the protein increase is usually much greater than in ruptured disk. The herniation may be visualized by x ray following air injection or more satisfactorily by lipiodol both of which methods demonstrate a filling defect due to the hernia As the favorite site of a ruptured disc is low in the lumbar spine every endeavor should be made to puncture the sac below the suspected level as the fluid below this usually shows elevated protein whereas above it may be normal Hence it is often wise to perform a double lumbar puncture in order to obtain fluid both from above and from below the supposed hernia normally the protein from these two loci will vary little but in the presence of herniated disc there will usually be a considerable difference Occasionally a puncture below a herniated disc shows block and very high protein This occurs only when the disc cartilage has protruded so far as to be almost free and is so large that it stimulates an extradural tumor in causing transverse caudal symptomatology

Lateral Sinus Thrombosis—A modification of the Queckenstedt test is applicable to the diagnosis of lateral sinus thrombosis In such a condition compression of the jugular vein on the side of the lesion fails to elevate the fluid in the spinal manometer whereas compression on the unaffected side causes an excessive elevation equivalent to that normally seen when both veins are compressed The fluid findings are otherwise not characteristic although they usually show evidence of mild aseptic meningitis In the case of a mural thrombus this test is of course less striking The test has been found more *reliable in sinus thrombosis of the right side* than of the left as would seem reasonable from the anatomic finding that the torcula most frequently turns to the right and appears to discharge more blood to the right lateral sinus

Chronic Degenerative Diseases of the Central Nervous System—In such diseases as progressive muscular atrophy amyotrophic lateral sclerosis and *syringomyelia* combined system disease no distinctive alterations of the spinal fluid have been found As a rule a slight to moderate increase in the protein content and the presence of an

occasional lymphocyte and granular phagocyte give the impression that a destructive process is present but the changes which we are able to demonstrate today are in no way pathognomonic

In *active progressive multiple sclerosis* a combination of findings is highly characteristic With considerable uniformity the pressure of the fluid is normal the dynamic conditions normal the protein content high normal or slightly increased (40–60 mg per 100 cc) a trace of globulin present the cell count slightly increased (15–30 lymphocytes) and the Wassermann reaction negative The colloidal reaction is however strong and in the gold sol test there is not infrequently a paretic zone While not pathognomonic this combination of findings occurs often in multiple sclerosis and almost never in other diseases It is therefore significant In inactive nonprogressive multiple sclerosis the fluid is normal or changed as in other degenerative diseases just described

Neuritis and Radiculitis—The spinal fluid in peripheral neuritis is normal When the neuritis involves the nerve roots however we find an increase in protein sometimes a very considerable increase Guillain s dissociation cyto albumineuse is characteristically found in radiculitis (infectious neuronitis) The same is true of diabetic neuritis

Cerebral Hemorrhage—When bloody or blood tinged fluid is obtained on lumbar puncture immediate steps must be taken to determine whether the blood is in the fluid as the result of some abnormality or as the result of faulty technic. This point may usually be determined by receiving the fluid into three or more test tubes which will be decreasingly turbid if from the technic of puncture If the fluid containing blood derived from a pathologic source be centrifugalized evidence of hemolysis will be seen in the supernatant fluid

Granting that the blood is found in equal amounts in a series of test tubes we can safely assume that the subarachnoid fluid has been previously contaminated with blood and that if no previous puncture has been performed the blood indicates hemorrhage somewhere in the neuraxis The age of the hemorrhage may be roughly estimated by noting the color as it changes from red to orange to yellow Evidence of such a hemorrhage will usually be found for two to three weeks

Hemorrhagic fluids are under increased pressure at least early and show a protein content consistent with the amount of blood present but usually more white cells than would be expected because of the meningeal reaction to blood

The pathologic significance of blood in the spinal fluid can often be estimated with considerable certainty If found in persons who have just received a head injury it may be assumed that the *bleeding is from pial vessels* with or without brain injury If found in a young person with no injury, one thinks first of *spontaneous hemorrhage from aneurysm* at the brain base in an older person with hypertension and arteriosclerosis the *hemorrhage is primarily cerebral* with rupture into ventricles or subarachnoid space

Two important types of intracranial hemorrhage may fail to show frank blood on spinal puncture namely arterial hemorrhage into the epidural space and venous hemorrhage into the subdural space Yet both may be suspected by an increase in fluid pressure In the case of *subacute and chronic subdural hematoma* however we find in half the cases a yellow tinted fluid under slight increase in pressure and containing a little elevation of protein without cells.

While it is quite certain that small vascular accidents may occur in the brain with no recognizable fluid accompaniments such lesions be they small hemorrhages thromboses or emboli are frequently suspected on finding slight elevation in pressure and protein

Communicating Hydrocephalus and Serous Meningitis—The outstanding features of communicating hydrocephalus and serous meningitis are the presence of an excessive amount of spinal fluid and a diminished concentration of the fluid The excessive amount of fluid (50–75 cc) may be estimated by measuring the amount obtainable (normally about 15–20 cc) with the patient in the lateral position An idea of the quantity may be obtained also by noting the rapidity of drop in pressure on withdrawal of known amounts Normally the pressure drops approximately 30 mm in the manometer after withdrawal of 10 cc When the quantity is

large the drop is much less perhaps 10 or 20 mm The Ayala index attempts to express this relationship in mathematical terms The lower concentration of the fluid is best demonstrated by the protein tests these may show almost no turbidity not infrequently so little that it cannot be accurately measured

Uremia Diabetes and Myxedema—In at least three diseases in which metabolism is markedly altered there are characteristic changes in the spinal fluid In uremia the nonprotein nitrogen content is elevated and in diabetes the sugar content is increased This increase is roughly in proportion to but never so great as that in the blood In nephritis and especially in uremia the pressure is likely to be high and the amount of fluid increased If vascular accidents have occurred the total protein content is also increased The fluid findings in myxedema are of interest showing moderately high pressure and increase in protein As these fluid findings are also seen in brain tumor this *similarity should be recognized*

Brain Tumor—Lumbar puncture in the presence of subtentorial tumor should be considered a dangerous procedure and should not be performed except as indicated below Lumbar puncture in patients with tumors above the tentorium is usually safe but frequently aggravates the symptoms and is therefore *not to be performed without consideration* It is probable that any physician who has had wide experience with lumbar puncture has had personal experience with or knowledge of death either immediate or within twenty four hours following withdrawal of fluid Usually the cause is a tumor in the cerebellar fossa which produces hydrostatic pressure and medullary paralysis by wedging the medulla in the foramen magnum

When it seems essential to examine the spinal fluid although a tumor may be present it is reasonably safe to tap the spine if there is no well marked elevation of the optic disks If the disks are choked however it is wiser to omit lumbar puncture entirely or perform combined ventricular lumbar punctures which provide more valuable information and are safer By this method the lateral *ventricle is tapped first* and the pressure lowered before lumbar puncture is performed Then manometers are attached and dynamic studies carried out as in the case of suspected spinal subarachnoid block With subtentorial tumor a partial ventriculo subarachnoid block is characteristic The only tumors above the tentorium likely to produce block are those obstructing the aqueduct of Sylvius *i e* tumors of the third ventricle, pontine gliomata and pineal tumors.

Pressure in the case of tumors varies greatly from high normal to the highest recorded in any disease (frequently 700–800 mm) depending on the size and situation of the tumor A pressure of 1000 mm has been reported In the early evolution of the tumor however, no general brain pressure is exerted, and therefore no increase in pressure is found in the cerebrospinal fluid so that a normal pressure must not be considered as inconsistent with the presence of brain tumor In brain tumor the fluid is usually colorless but slightly yellow fluids are occasionally obtained usually in the case of subtentorial localization Rarely a supra *tentorial glioma with cystic degeneration* will give a yellow discoloration of the spinal fluid

One type of tumor characteristically yields a high protein titer *i.e* the acoustic neuroma Not infrequently the fluid is yellow As tumors of the cerebellum do not as a rule give such a fluid we have in the fluid examination a differential point of some value The safety of lumbar puncture is the presence of any brain tumor should be questioned especially in subtentorial tumors for in such tumors the possibility of medullary herniation into the foramen magnum is especially to be feared Therefore the physician should duly consider the advantages of the fluid examination as compared with the dangers of puncture in such cases

The protein content of the fluid also varies. It is most often just above normal (50–60 mg) but may reach 100 to 200 mg per 100 cc especially with subtentorial tumors In such patients there is a sharp contrast with the low protein content of the ventricular fluid and dynamic evidence of block is of importance in localization

Often no cells are found. More frequently a few arachnoid cells and lymphocytes give evidence of local irritation or degeneration occasionally all counts comparable with

those of aseptic meningitis are encountered Rarely have tumor cells been reported

There is usually an abnormal reaction in all colloidal tests but there is certainly no distinctive zone in the benzoin mastic or gold sol reaction

The Wassermann reaction is said to be occasionally positive with tumor but it is usually negative An unrecognized, associated syphilitic process is a reasonable explanation for this rare anomaly

On the whole the evidence obtained from lumbar puncture in a brain tumor suspect is likely to be less than hoped for and with the known danger already emphasized above is not to be performed without satisfactory reason Fluid analysis has proved of considerable value in three situations (1) when a brain tumor and vascular lesion of the brain cannot be differentiated elevated pressure and protein favor tumor (2) when tumor and syphilitic meningitis are indistinguishable, the cell increase and Wassermann reaction will settle the question (3) when acoustic neuroma is suspected a high protein and often yellow fluid will give added support to this diagnosis

Significance of Normal Fluid Findings —If the cerebrospinal fluid pathways be patent it is most unlikely that an inflammatory lesion or a space constricting tumor of any size can be present without accompanying change of some sort in the spinal fluid Small lesions must be excepted in this general statement such as certain vascular lesions mentioned above Likewise we have no criteria on which to base a diagnosis of the various degenerative processes These must be studied by pneumo encephalography a subject not here considered

Even in the case of certain expanding lesions of the cranium we must not be too dogmatic in our primary statement for not infrequently a tumor of the frontal lobe a large subdural hematoma or an abscess of considerable size, has been found present where fluid pressure and all tests were considered normal Nevertheless the significances of positive and negative findings alike are so often of importance that evaluation of the spinal fluid must be considered of prime importance in the diagnosis of obscure diseases of the nervous system

JAMES B AYER

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

(Meningovascular Tabetic and Paretic Neurosyphilis Congenital Neurosyphilis)

Neurosyphilis' is a general term which includes all those disorders of the nervous structures the envelopes surrounding them and the blood vessels traversing them which are caused by the *Treponema pallidum* The organism usually invades the nervous system early in the course of syphilis although symptoms may not appear for many years. The symptoms may be of almost any variety but may logically be considered as variations of a common disease caused by a single type of organism The clinical manifestations depend on the localization of the virus and the pathologic changes which in turn depend on the inherent reaction of the tissue invaded In 1913 when the *T pallidum* was found in patients with general paresis and tabes dorsalis evidence that these syndromes are types of neurosyphilis seemed to be complete At the same time, the concept of parasyphilis lost much of its meaning and with more satisfactory methods of treatment it is no longer necessary to consider it

The brain and spinal cord are composed of neurons and neuroglia cells Both are formed from the ectodermal layer The neurons form the true parenchymatous tissue The meninges* and blood vessels are derived from the mesoderm and are in no sense true nerve tissue but because of their close anatomic relationship with the brain and spinal cord any pathologic changes in them directly influence these latter structures From the viewpoint of morbid anatomy clinical symptomatology and response to antisyphilitic therapy it is convenient to think of neurosyphilis as being predominantly meningeal vascular or parenchymatous Such is the basis of the following discussion

Etiology —The *Treponema pallidum* is the cause of all neurosyphilis While the disease is generalized (primary and early secondary period) and the entire body is being invaded by the spirochetes the central nervous system rarely escapes This is evidenced by the symptoms the serologic changes and

* Recent work of Harvey suggests that the pia-arachnoid is of ectodermal origin

the presence of the spirochete in the cerebrospinal fluid In many cases the central nervous system apparently becomes sterilized and undergoes no later change but in 30 to 40 per cent this reaction of immunity is lacking or only partial and the spirochetes remain present within the central nervous system only to produce symptoms in later months or years Why some infected patients develop active neurosyphilis and the majority escape has been explained in several ways but no explanation is scientifically proved or free from doubt For example it has been stated that the *incidence of neurosyphilis* depends on the constitution and heredity of the individual affected and studies have been made which purport to show that neurosyphilitics are of the neurotic type Bolton claims that the histologic brain pattern which permits general paresis to develop can be recognized The theory that a particular strain of spirochetes has a definite neurotropism has also been advanced by numerous observers and there are several famous instances of the development of paresis or tabes in different individuals infected from the same source Conjugal neurosyphilis is relatively frequent Experimental evidence that there is a difference in the reaction of spirochetes taken from the fresh chancre and from the brain of the paretic has been obtained by Levaditi and A Marie Their evidence however is not free from criticism Another theory is that the condition of the patient at the time of his infection and the character of his immunity responses are all of primary importance. This latter view seems to be the best at the present time if only because it leads to thorough investigation of the nervous system in every syphilitic patient regardless of the stage of the disease

Symptoms.—The symptoms characteristic of early neurosyphilis of all types are headache due usually to the meningitis vertigo blurring of vision and mild optic neuritis None is necessarily present The spinal fluid during the primary and early secondary period frequently undergoes mild changes Its lymphocytic content increases globulin is present the gold sol reaction changes and the Wassermann reaction may be positive All these abnormalities may occur together At times the Wassermann reaction of the spinal fluid is positive before that of the blood becomes positive Spirochetes which could be grown in animals have been recovered from the spinal fluid in the very earliest stages of the disease As a rule the symptoms disappear either with treatment or spontaneously in much the same manner as does the skin roseola a fact probably to be accounted for by the immunity which the patient develops

Types—*Meningovascular Neurosyphilis (Cerebral Syphilis Spinal Syphilis Cerebrospinal Syphilis Syphilitic Meningitis Cerebral Gumma* etc) —DEFINITION.—Meningovascular neurosyphilis is an involvement of the membranes and vessels of the nervous system by the *Treponema pallidum* with or without secondary involvement of the nervous parenchyma Although it is usual for both meninges and blood vessels to be involved there are many instances where one or the other is predominantly affected and not so rarely there is almost exclusive involvement of either structure

INCIDENCE.—The condition is said to develop usually within the first five or six years after infection but is not rare many years later and is associated with congenital as well as with acquired syphilis No very definite statements can be made about the incidence of the various types of meningovascular neurosyphilis but it may be stated that approximately 20 to 30 per cent of all patients with syphilis develop meningovascular symptoms

MORBID ANATOMY —In the vast majority of cases the primary pathologic changes occur in the meninges and blood vessels and are therefore similar to the syphilitic lesions in other mesenchymal tissues In the *meninges* the reaction is of an exudative nature and the tissue is invaded by inflammatory cells for the most part by small lymphocytes but also by a few large lymphocytes and endothelial cells and an occasional plasma cell. The lesion is chiefly in the pia arachnoid although at times the dura is also involved In the very acute fulminating condition which is quite rare polymorphonuclear leukocytes may make up to 50 per cent of the infiltrating cells The meningitis may be somewhat localized or so extremely diffuse as to affect all the cerebrospinal meninges In the mild type the infiltration

is only slight, but it may become extremely marked The macroscopic picture of the pia of mildly affected patients is almost normal, a slight haziness being the only visible change If the lesion is more marked the membranes may be greatly thickened, have a matted appearance and occasionally even resemble creamy pus The very large gummatous lesions which may develop are similar to the gummatous tumors seen in other parts of the body Although the most frequent site of the meningitis is the base of the brain and the thoracic portion of the spinal cord other parts of the meninges may also be involved Individual nerve fibers may be surrounded by the exudate and compressed, and when the basal meningitis is relatively severe several nerves may be affected At times the spinal meningitis is so intense that the circumference of the cord is greatly compressed with consequent degeneration of the fiber tracts

Cerebral irritation may result from meningitis of the convexity Optic neuritis sometimes follows invasion of the pia in the region of the optic chiasm In certain acute conditions the cerebral cortex is involved by extension the spirochetes invading the cortical tissue and causing an encephalitic complication

The lesions of the cerebral *blood vessels* are similar to the vascular changes in other parts of the body the perivascular sheaths being infiltrated with lymphocytes There is some question whether the process starts in the intima, media, or adventitia but it is probable that the media undergoes the first change The relation of the coats becomes altered and because the elastica splits and the intimal lining is broken thrombi frequently form This is the most common serious vascular accident of neurosyphilis although at times hemorrhages occur from the weakened vessels

The spirochetes are relatively easily obtained from the lesions of the more acute types of meningitis and meningo encephalitis, on the other hand it is impossible to recover them from those of the chronic type and from gummata

Symptoms.—The symptoms of meningovascular neurosyphilis vary greatly according to the location and extent of the lesion the relative severity of the meningeal and vascular changes and the extent of the pathologic process One should always keep in mind that meningovascular neurosyphilis may simulate any form of nervous or mental disorder and produce symptoms resembling those of any neuropsychiatric condition

Although symptoms may develop within the very earliest period of the syphilitic infection or not appear until forty years or more after the primary stage, certain manifestations have come to be associated with the different stages of the disease. In the first weeks of the syphilitic infection the symptoms of cerebrospinal involvement are usually quite mild and consist chiefly of headache (probably due to meningeal irritation), tinnitus aurium vertigo, and blurring of vision At times pains may be caused throughout the body by irritation of the spinal nerves Ophthalmoscopic examination frequently reveals papillitis During this period however there may be symptoms of a very severe cerebrospinal meningitis with intense headache rigidity of the neck Kernig s sign and complete prostration Such a syndrome requires prompt and vigorous antileutic treatment

In the period beginning six months to a year after the primary stage severe meningovascular disasters including meningo encephalitis occur with relative frequency The meningitis may be either cerebral or spinal A palsy of one or more of the cerebral nerves may develop which is fleeting and disappears within a few days or may be more permanent When it is of very short duration recurrences are frequent Headache dizziness and visual and auditory symptoms are often noted Spinal cord symptoms are less frequent, but may develop as rheumatic pains in any part of the body and occasionally as disturbances of the sphincters Very marked spinal meningitis at the dorsal level sometimes leads to compression of the cord or to so called transverse myelitis with resulting spastic paraplegia Erb considered the syphilitic spastic paraplegia which bears his names as a primary degeneration of the corticospinal tracts but it is doubtful if such an entity exists because the few cases that have been studied pathologically show compression of the cord by the meningitis Gummata are quite infrequent in the first year

The *vascular disorders* are the most dreaded complication of the early period Thrombosis of one of the large meningeal or cerebral vessels is not infrequent The sylvian and lenticulostriate arteries are particularly susceptible to this lesion this results in hemiplegia These apoplectic conditions often come on without warning or on the contrary the patient may awake after a few days of headache and dizziness to find himself paralyzed. The paralysis is the result of a destruction of brain tissue due to the shutting off of the blood supply Although this condition usually develops during the first five to seven years after infection the syphilitic patient is liable to such manifestations of meningovascular syphilis throughout life

SEROLOGY —During the primary and early secondary period of mild neurosyphilis the changes in the spinal fluid are relatively insignificant Occasionally the Wassermann reaction in positive but more frequently there is slight pleocytosis (10–25 cells per cubic millimeter) A little globulin may be present, and there may be a weak gold sol reaction The blood Wassermann is negative during the early part and positive during the latter part of the primary period In the early secondary period of very mild cases the spinal fluid is very similar to that found during the primary stage while the Wassermann reaction of the blood is usually positive

In patients with symptoms, the reactions of the spinal fluid are likely to be rather strong after a few months. In most instances the Wassermann reaction is positive with 1 cc of fluid The cell count may be quite high (20–200 cells per cubic millimeter) and when the meningitic symptoms are relatively severe may run up into the thousands The fluid nearly always contains globulin and an increased quantity of albumin The gold reaction usually follows the so called 'luetic curve At times the serologic reactions may be strongly positive and resemble those of paretic neurosyphilis

If the lesions are chiefly vascular the serologic findings may be the same as those of the meningeal form but often they approach normal

Prognosis—Although the prognosis of meningovascular neurosyphilis is better than that of any of the other types of the disease no general statement can be made because there are so many different manifestations of the condition and the changes vary so greatly in the different stages The outlook for patients with meningeal lesions, whether early or advanced is usually excellent if treatment be adequate For those with fulminating neurosyphilis it is very doubtful even with the best of treatment, and if adequate and active therapy be omitted the prognosis is hopeless Of the strictly vascular conditions there are two types one which becomes manifest at an early period and may be so arrested by suitable treatment that there are no further vascular changes and another which appears at a later stage and responds to therapy less satisfactorily because the vascular lesions are more generalized Most patients however do improve greatly after treatment

Tabetic Neurosyphilis (Tabes Dorsalis Locomotor Ataxia Syphilitic Posterior Spinal Sclerosis) — DEFINITION — Tabetic neurosyphilis is an infection characterized by visceral crises and symptoms referable to the afferent spinal nerves and the nerves of special sense The kinesthetic and pain fibers are as a rule first affected this leads to progressive loss of position sense and to lancinating pains Trophic disturbances and disorders of the cerebral nerves are also frequently associated with the condition

MORBID ANATOMY —There is a degeneration of the posterior columns of the cord of the posterior roots and to some extent of the posterior ganglia Sometimes the optic nerve degenerates and other sensory nerves may be involved Meningitis generally of a mild chronic type usually accompanies tabes dorsalis

PATHOGENESIS —There is a general belief that the pathologic changes in tabes originate in the intradural portion of the posterior root. The French school has called attention to the possibility that the lesion may start in the posterior ganglia The degeneration of the cells of these ganglia is however rarely sufficient to explain the degree of degeneration within the posterior root Much notice has also been given to the idea that a toxin circulating in the spinal fluid affects the posterior root but this theory has been rendered less acceptable by

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brought down unsteadily as if being slapped on the floor This latter condition is characteristically tabetic.

During the early stages there is little if any loss of the tactile, pain or temperature *senses* Hyperthesia and hypalgesia develop later Hyperesthesia, especially of radicular distribution is quite common Rarely, in the late stages complete anesthesia develops and is followed by disappearance of the pain which may have been very severe The loss of kinesthetic sense as shown by inability to feel passive movements of the toes or fingers may be noted quite early

The *visceral crises* are relatively common manifestations. That most frequently seen is the *gastric crisis* which is characterized by recurrent abdominal distress and vomiting often associated with considerable pain in the abdomen The attacks come on without relation to food and may persist for hours or days at a time After the crisis has passed the patient feels well and has no gastro intestinal symptoms The attack may be extremely severe and controlled only by large doses of morphine The character of the crises varies greatly Some patients have mild nausea and distress while others vomit almost continuously This manifestation is not related to the general function of the gastro intestinal tract and gastric analyses and x ray studies are entirely negative in the typical uncomplicated case Since in some patients gastric crises are accompanied by no other troublesome tabetic symptoms and the reflexes may be quite normal some authorities consider the gastric crises a separate syndrome

Crises of other organs also occur Those in the rectum are characterized by diarrhea or tenesmus, those in the larynx by local spasm

Disorders of the sphincters are at times the first symptoms Incontinence of urine usually beginning as dribbling with great difficulty in starting the stream and inability to completely empty the bladder is a very common symptom The bladder has reduced tone dependent on loss of sensation and is readily recognized on cystoscopy as a spinal cord bladder In relatively few cases there is also loss of control of the rectal sphincter Loss of sexual power is a frequent and often an early symptom

Atrophy of the Nerves of Special Sense — Mild *optic atrophy* occurs in many cases of tabes that leading to marked diminution of vision or complete blindness however develops in about 10 per cent of all tabetic patients and may be an early or almost isolated symptom Like gastric tabes it may occur without the usual cord signs and symptoms and is often designated as optic tabes. The *auditory nerve* is sometimes similarly involved but marked degeneration is less frequent Symptoms depending upon atrophy of the *other nerves of special sense* are rare

Although *trophic disturbances* usually appear during the very late stages *Charcot joints* may develop at any period occurring most often in weight bearing joints *e g* hip knee ankle and spine The lesion is to be looked upon as the result of repeated traumata to the joint surface due to lack of sufficient joint sensation and consequent deficient muscular protection. *Perforating ulcers* which were formerly seen quite frequently are now extremely rare possibly because of modern methods of treatment

The most important *neurologic signs* are (1) absence of the knee jerks and ankle jerks and less frequently of the tendon jerks of the upper extremities (2) the Romberg sign (3) ataxia of the legs and less often of the hands (4) pupillary changes irregularity inequality sluggishness and the typical Argyll Robertson condition (5) loss of control of the sphincters and sexual impotence (6) sensory disturbances such as hypesthesia and even anesthesia and (7) Charcot joints

The *tendon reflexes* are typically lost early frequently before the appearance of any symptoms Their absence is caused by interruption of the reflex arc when the fibers of the posterior roots are destroyed Those of the lower extremities often disappear while the reflexes of the upper extremities are retained although when the upper part of the cord is involved the reverse is true The ankle jerks are frequently lost before the knee jerks. In many cases of tabes the reflexes are retained especially when there is evidence of gastric crises or optic tabes The *skin reflexes* may be present or absent The *abdominal reflexes* are likely to be absent as they are in other forms of syphilis

the more modern conception that all the morbid changes of neurosyphilis are caused by the activity of the spirochetes rather than by their toxin The fact that meningitis practically always develops has evoked the suggestion that the posterior root is pinched in the inflammatory process (compare with cerebral nerve palsies due to basal meningitis) but this does not explain the relatively infrequent involvement of the anterior roots

The work of Richter seems to demonstrate that the tabetic lesion is due to the activity of the spirochete itself and that the local change consists of a specific granuloma in the posterior root Richter has apparently succeeded in his attempt to show that the meningitis is a secondary and not a primary tabetic lesion or in other words that tabes may exist without meningitis The anatomic relationship as first pointed out by Nageotte is such that there is a more acute angle made by the posterior root and the meninges than by the anterior root According to Richter this offers a recess with less fluid in circulation in which the spirochetes can locate and this accounts for the greater frequency of involvement of the posterior than of the anterior root He points out however that the latter is affected late in the disease He has been able to demonstrate the presence of spirochetes in what he describes as a definitely specific granuloma of the posterior root This theory seems to be the most satisfactory and coincides most nearly with the present concept of the parasitology of syphilis

SYMPTOMS AND SIGNS—Most of the typical signs and symptoms of tabetic neurosyphilis appear only after the disease has persisted for some time and relatively few develop during the very early stages or in atypical conditions In the early stages tabes may be of two types in one the symptoms develop before the neurologic signs in the other the signs are the first to appear In fact in one group of patients the neurologic findings may be very nearly normal while there are such typical symptoms as lancinating (rheumatic) pains gastric crises and other visceral crises The diagnosis is confirmed by the spinal fluid findings In another group Argyll Robertson pupils and the absence of the tendon reflexes may be obvious before any symptoms develop

Of the characteristic *symptoms* the most common are related to the sensory system and are apparently caused by pathologic change in the posterior roots These symptoms are of the type of painful sensations or kinesthetic abnormalities the latter of which lead to motor incoordination The cerebral nerves of special sense especially the optic are often involved with subsequent symptoms such as blindness and deafness Visceral symptoms such as gastric rectal and laryngeal crises which are common probably depend on disorders of the sympathetic and autonomic fibers Trophic changes (perforating ulcer and Charcot joint) also occur

Pain which is the most common of the early symptoms usually begins in the legs and sooner or later becomes very severe It is often described as a burning gnawing or lancinating sensation such as might be produced if a hot knife were stuck into the flesh and twisted The attacks which come on with lightning like rapidity last for hours and are followed by only a brief interval of freedom Such attacks may recur throughout many years In some instances there is a sensation of constriction about the waist or chest (girdle sensation) which follows involvement of the radicular nerves Associated with the attacks are all sorts of abnormal sensory phenomena such as paresthesia numbness and sensations of cold warmth or tingling When the pain is very severe pressure on the skin may give relief or be intolerable because of the exquisite sensitiveness Occasionally ecchymoses appear on the skin in the region where the pain is felt.

Ataxia (incoordination), the result of loss of the fibers of the posterior roots and posterior columns often appears after the onset of the pain although it may be the earliest symptom and be unassociated with any other disorder of sensation It usually involves the lower extremities but occasionally affects the hands when the cord lesions are cervical The change of gait which usually develops slowly is ordinarily first noticed when the patient is *walking in the dark* Once in a while the change comes very suddenly The abnormality varies from a slight unsteadiness in the early stages to a marked change of gait in the late stages in which the foot is thrown into the air and

Pachymeningitis haemorrhagica is occasionally present The pia arachnoid becomes more or less thickened especially over the frontal regions and is usually milky or translucent Frequently, cerebrospinal fluid accumulates between the pia and the cortex as a result of cerebral atrophy The cerebral atrophy is most prominent at the frontal poles where the lesions are most marked and is manifested by widening of the sulci and flattening of the convolutions The ventricles are usually enlarged and ependymitis or roughening of the fourth ventricle is usually visible

Microscopically, the disease is characterized by degeneration of the nerve cells especially in the frontal region and as the disease progresses or in aberrant types in any part of the cortex cerebellum or bulb The structure of the cortex is greatly disturbed All types of pyknotic changes are present Completely degenerated cells are in close proximity to well preserved cells Gliosis compensates in part for the loss of nerve elements Satellitosis and phagocytosis occur and rod cells are often present. Perivascular infiltration of the small vessels of the cortex white matter and pia with lymphoid cells is always present Most striking and most characteristic is the presence in the tissue of plasma cells which in some instances form the majority of the infiltrating cells It is usually said that new blood vessels form in the affected areas Subependymal glia proliferation occurs in the ventricular areas and is most evident in the floor of the fourth ventricle Vascular sclerosis of the larger vessels is not a part of the paretic process and is to be considered a complication Degeneration of the fibers of the projection system results from the neuronal loss so that in late cases there is often degeneration of the corticospinal tract Tabetiform lesions of the cord are common

SYMPTOMS—The symptoms of paretic neurospyhilis are protein in character and form almost any syndrome. The onset is at times insidious at other times sudden For systematic discussion the mental symptoms may be divided into three groups (1) those of the period of onset often spoken of as the medico legal state (2) those of the period of full development of the disease and (3) those of the terminal period in which the patient is bedridden Such a division is entirely arbitrary and in many cases impracticable A galloping form of the disease is described which progresses very rapidly and leads to death within a short period

1 *The Early Stage*—Any *change in the personality of an adult* should arouse suspicion of paretic neurosyphilis The first changes in character may be very slight and of brief duration, a slight change in manner for instance greater irritability carelessness about the clothes and person lack of judgment absent mindedness, inability to concentrate increased fatigability hypersuggestibility and slowness of comprehension These symptoms may develop very early and be of very little apparent significance in themselves They may, however, lead to such disasters as heavy losses in business alcoholism and loss of reputation because of various excesses Very frequently *neurasthenic symptoms* develop into mild depression or on the other hand into euphoria and elation These symptoms may become much more marked after a period of days, weeks months or even years and lead to symptoms characteristic of the well established phase of the disease

The early physical signs and symptoms include headache visual disorders and loss of weight Often there is a slight disturbance of manual dexterity *i e* tremors of the outstretched hands and inability to make coordinated movements The frequent decrease of muscle tone especially of the face results in flattening of the nasolabial folds which reduces the facial expression and markings and often makes the patient appear younger than he is Another characteristic symptom is a speech defect which causes poor enunciation of such test phases as Methodist Episcopal third riding artillery brigade etc

The *pupillary changes* of neurosyphilis appear in the paretic form as in all others The typical Argyll Robertson pupil can only infrequently be seen In the early stage the reaction of the pupils may be quite normal or the dilated pupil may respond poorly to light. Later there is no reaction to light but there is response to accommodation and finally both types of reaction are lost

probably also because of interruption of the reflex arc in the posterior roots The *cremasteric reflexes* persist except in unusual or advanced conditions

The noteworthy *Romberg sign* (inability to maintain equilibrium with eyes closed and feet placed close together) may be observed before the patient has noticed any difficulty in walking because of the reduction of the normal flow of impulses from tendons and joints which are essential for reflex standing

Pupillary Signs—As in other types of neurosyphilis irregularity and inequality of the pupils are common early signs The pupils are almost always unequal and their early sluggishness of response usually increases until they are of the typical Argyll Robertson type *i e* respond in accommodation but not to light This type of reaction is seen more commonly in tabes than in any other form of neurosyphilis The pupils may be so contracted that their diameter is less than that of a small pin head but they may also be quite large. In not a few cases they become fixed and react to neither light nor accommodation

Motor Palsies—Paralyses of the extrinsic eye muscles especially the levator palpebrae and the external or internal recti may be the first manifestation of tabetic neurosyphilis to attract the patient s attention Such palsies may occur years before any of the other characteristic symptoms of tabes They are usually temporary lasting for a few days or weeks but are sometimes permanent As a rule they are accompanied by reflex anomalies in other parts of the body which are revealed by examination Lid drop or diplopia often precedes by several years the symptoms of which a tabetic patient complains but since these conditions right themselves rather promptly they are often not seriously considered Muscle tone is generally decreased in the extremities affected because of the reduction of afferent impulses to the cord Joint capsules are relaxed and increased mobility of the joints can be demonstrated

In the late stages of the disease the intrinsic muscles of the hand or foot may become wasted and also although more rarely the larger muscles This may result from degeneration of the anterior horn cells pinching of the anterior root by the meninges or, as Richter suggests from degeneration of the anterior root caused by spirochetal action at the junction of the anterior and posterior roots

SEROLOGY—Probably in the tabetic type as well as in the other forms of neurosyphilis changes take place in the spinal fluid before either signs or symptoms of the disease become manifest The reactions of the blood and spinal fluid in tabetic neurosyphilis are very similar to those in the meningovascular type Not infrequently the spinal fluid resembles that recovered from paretic patients and occasionally it is entirely negative apparently because of spontaneous arrest a condition which leads to the concept of a burned out process

DIAGNOSIS—Serologic tests usually permit recognition of tabetic neurosyphilis before the appearance of marked symptoms and signs Consequently when laboratory methods of diagnosis are employed and modern treatment is promptly instituted fewer cases are allowed to assume the typical characteristics It is well to bear in mind that a typical case is relatively far advanced and is past the stage in which the clinician can take pride in making a diagnosis

PROGNOSIS—Without treatment the symptoms usually increase slowly for many years until the patient finally becomes bedridden Frequently however the progress is so very slow that the change from year to year is only slight On the other hand symptoms may develop very rapidly Under treatment improvement is the rule and occasionally arrest of the progress occurs spontaneously

Paretic Neurosyphilis (General Paresis General Paralysis General Paralysis of the Insane Dementia Paralytica)—DEFINITION—Paretic neurosyphilis is a chronic syphilitic meningo encephalitis characterized by progressive dementia and a diffuse generalized paralysis which terminates in death

INCIDENCE—About 3 per cent of syphilitic patients develop symptoms of paresis They occur approximately three to five times as frequently in men as in women although the incidence of luetic infection is not greatly different in the two sexes

MORBID ANATOMY—In paretic neurosyphilis there is characteristically a macroscopic thickening of the dura which is frequently adherent to the calvarium.

ated with atrophy of the anterior horn cells The clinical diagnosis depends on the neurologic signs of neurosyphilis and the changes in the spinal fluid

Syphilitic epilepsy is not a well defined syndrome and there is much discussion concerning its existence. *Three types* are described in the first though there is no pathologic or serologic evidence of neurosyphilis epileptic seizures develop some time after the syphilitic infection of an individual supposedly without hereditary epileptic taint who has never had previous convulsions the second type is supposed to be related to meningo vascular neurosyphilis and is apparently the result of irritation of the brain, in the third type there is a parenchymatous disorder of luetic origin In the two latter there is the suggestion of an etiologic connection between the convulsions and syphilis in the first, such an hypothesis has little foundation It is true that epileptiform seizures are not rare in all types of cerebral neurosyphilis but the recurrence of convulsions over a period of years is very uncommon

Syphilitic paranoia is described in the German textbooks as a condition in which the patient has the clinical evidence of paranoia in conjunction with syphilis or neurosyphilis It is even less well established than the syphilitic epilepsies.

Syphilis of the peripheral nerves may be secondary to disease of such nearby structures as bones fasciae and muscles Gummata may encroach upon and implicate the nerves The peripheral nerves may however be affected by a direct extension of the inflammatory reaction along the lymph channels and perivascular spaces Such neuritis is known to cause palsy of motor nerves or in the case of the sensory nerves neuritic pains

Congenital neurosyphilis closely simulates all the syndromes of acquired neurosyphilis. Only too frequently the nervous involvement of congenital syphilis is not recognized during the early years of the patient s life Recent studies have shown that about 20 per cent of the patients with congenital syphilis show clinical or serologic evidence of neurosyphilis Symptoms may make their appearance in the first years of life or may be delayed until adolescence when they suggest meningovascular, tabetic, or paretic neurosyphilis

Juvenile tabetic neurosyphilis is very unusual The symptoms are quite similar to those of the acquired form except that pains are perhaps less frequent.

Juvenile paresis is relatively very frequent as compared with juvenile tabes (50 1 in the author s series) The usual age of onset is between twelve and eighteen years The patient may have appeared to be quite normal before the paretic symptoms develop showing few if any stigmata of congenital syphilis The characteristic clinical manifestation is usually dementia which progresses rather rapidly Occasionally the symptoms are those of grandiosity In other instances the child fails to develop mentally and is considered feebleminded The duration of life is usually from three to five years after the onset of mental symptoms

The serology of all juvenile neurosyphilis is identical with that of the acquired form

Syphilitic feeblemindedness is described in many textbooks but the author has not recognized such an entity Unless there is definite luetic involvement of the brain the juvenile syphilitic usually has the mentality characteristic of his family

Diagnosis —As the various syndromes of neurospyhilis simulate almost any organic or functional disease of the nervous system it is necessary to consider the possibility of the disease whenever neuropsychiatric signs or symptoms develop The history of syphilis and examination of the blood and spinal fluid usually suffice for diagnosis of neurosyphilis It is unusual and rare for the serology to be negative Frequently it is only by examination of the spinal fluid that diagnosis is possible When the serology is negative the diagnosis of neurosyphilis is permissible only if the symptoms are very characteristics since experience has shown that such conditions are usually nonsyphilitic. It is nearly always advisable to confirm the clinical diagnosis by examination of the spinal fluid

Differentiation of the various forms of neurosyphilis is made by the symptoms and to some extent by the condition of the cerebrospinal fluid Even pathologically however it is not possible to distinguish all types Thus syphilitic meningitis may simu

Changes in the *tendon reflexes* are common Atrophy of the efferent or afferent pathways may be so balanced as not to alter the reflexes or may increase diminish or destroy them As a rule the changes of the tendon reflexes are relatively late manifestations although they may take place before the onset of any other recognizable symptoms The Babinski sign ankle clonus and other pathologic reflexes are to be observed in the early stage but are usually associated with atypical conditions or vascular complications late in the disease they are common In the early stages the sphincters are rarely involved and there is often increased sexual potency

Sometimes the period of onset is short and the disease attains the fully developed stage with great rapidity, in fact a seizure may occur in a person in apparently good mental and physical condition and be followed by well developed symptoms of the established stage The progress may however be so slow that a year or more elapses between the onset of mental symptoms and the development of the characteristic syndrome

2 The *stage of full development* is characterized by varied symptoms which may mimic any type of mental disease Typically there is *euphoria* and the patient is grandiose elated with delusions of wealth and great prowess and feels better than ever before This classic syndrome appears in only 10 to 20 per cent of cases Another type is that of *depression* with anxiety fear of impending danger and self accusation A third well recognized syndrome is that of a *simple dementia* in which without either excitement depression or delusion formation the mind of the patient deteriorates In a fourth form *paranoid ideas* predominate There are many other variations which need not be mentioned here

Common to all the forms and of the greatest importance is the *progressive dementia* Loss of memory especially for recent events later for past events as well difficulty in calculation and writing and defects of judgment are sooner or later apparent

Paretic seizures of either the epileptiform or apoplectiform type which are frequently accompanied by transient paralyses are characteristic of this stage The defect of speech is more marked and the disorders of the reflexes become quite prominent

3 *Terminal Stage*—In the third stage physical weakness becomes very great The patient becomes bedridden and finally reaches the condition of a vegetative organism There is emaciation bed sores develop and generalized paralysis of all the muscles of the body ensues If death is not caused by a seizure or by intercurrent disease it finally results from paralysis of the respiratory muscles

Prognosis—Paretic neurosyphilis has in the past been considered invariably fatal but at the present time the prognosis is more hopeful because of the newer forms of therapy Untreated patients who still are far more numerous than those who receive adequate treatment live on the average two and one half to three years after the onset of definite symptoms Some patients however die in a seizure at the very onset of the disease others linger for five to six years and very exceptionally a patient lives as long as nine or ten years

Spontaneous remissions are characterized by improvement of both the mentality and the physical condition of the patient This may be so great as to allow the patient to return to his former occupation These remissions usually last no longer than six months very rarely they continue for a year In a few cases they have been reported to persist for a period of years Spontaneous remissions occur in 2 to 10 per cent of patients Patients *treated in the early stages of paresis* by fever or with tryparsamide or a combination of the two have shown remissions in 30 to 40 per cent of cases Another 20 to 30 per cent are apparently arrested but with considerable deterioration The accumulated evidence now is sufficient to show that very beneficial modification is possible and that the prognosis is less serious than it was previously

Syphilitic Spinal Muscular Atrophy—A quite rare form of neurosyphilis is that in which degeneration of the anterior horn cells of the spinal cord produces the syndrome of progressive spinal muscular atrophy The lesion consists of perivascular infiltration with lymphocytes and plasma cells and meningitis similar to that of tabes associ

presents a different therapeutic problem The author is firmly convinced that no definite generalization is permissible and that the routines supposed to be applicable to many different types of cases are *illogical* and reprehensible The following outline of some very fundamental principles of treatment is based entirely upon the author's personal experience and may not agree at all with the beliefs of various authorities

Care of the *general hygiene* of the patient is one of the important features of the treatment of all types of neurosyphilis Many individuals improve when they have plenty of rest, fresh air and good food receive hydrotherapy and have their somatic defects corrected Coordination exercises are of the greatest importance at the ataxic stage of tabes and often bring marked symptomatic improvement

Fever and *tryparsamide* are the two main reliances in the treatment of the more serious types of neurosyphilis These methods have now thoroughly established themselves and over a period of approximately a score of years have been found to give rather consistent results Their value can be best considered in relation to the treatment of general paresis which previous to the introduction of these methods was almost out of the field of therapeutics. With the use of either *fever or tryparsamide it is possible to arrest* the active progress of the spirochete in at least 70 per cent of the cases Approximately 30 to 40 per cent make improvement clinically sufficient to return the patient to his former place in society and in approximately an equal number there is evidence of an arrest of the process as shown by cessation of the progress of the disease or by serologic criteria The results are very much the same with either method but fever has the advantage of working more rapidly Certainly the combination of fever and tryparsamide affords the best chance of success and the combined use is advisable both from the standpoint of doing as much as possible for the patient and because the continuing use of tryparsamide affords a greater guarantee against the relapse

There are a number of methods of involving fever for therapeutic purposes The one that has been used most extensively is *malaria* In usual practice the *Plasmodium vivax* the organism of tertian malaria, is employed as being mildest and most easily controlled In some cases where the patient is immune to this organism a quartan strain *may be preferable The only practical way* at present of transmitting the disease is from patient to patient In institutions which treat a good many such patients it is possible to keep a constant supply of infected patients as sources from which blood can be obtained for the inoculation of others As a rule eight to ten paroxysms are considered a sufficient course of malarial fever although occasionally fewer attacks will produce adequate results and at other times more paroxysms are allowed to the patient

Fever produced by *mechanical modalities* such as hot moist air boxes inductothermy warm water sprays etc is well standardized and allows for the development and maintenance of any temperature level desired The advantage of mechanically produced fever is that it is somewhat safer than malaria and can be given one day a week allowing a patient to continue his occupation on the other days This type of treatment requires an elaborate set up with experienced physician and technician Opinions differ as to the relative therapeutic value of malaria and mechanical fever

Fever may be produced by the *intravenous injection of typhoid vaccine* by certain *sulfur preparations* and other *protein shock methods* By and large these latter methods are not by any means so valuable as either the malaria or mechanically produced fevers

Following the course of fever it is the custom of many clinics to give weekly injections of tryparsamide either in courses of ten to twelve injections followed by a rest period or more or less continuously until the spinal fluid has become negative

It is logical to assume that these methods would be relatively more successful in the treatment of the less recalcitrant types of neurosyphilis than in general paresis As a matter of fact in the meningeal and meningo vascular neurosyphilis where there is not too much vascular degeneration tryparsamide aided by arsphenamine and bismuth has such a high degree of efficacy that fever is hardly ever required In fact in the relatively pure cases of meningeal syphilis the arsphenamines or bismuth are capable

late the tabetic condition in spite of a quite different course, it is then known as 'syphilitic pseudotabes' Likewise the meningovascular type may be erroneously diagnosed as paresis and *vice versa.*

Tables 1 to 4 outline the changes usually found in the spinal fluid in the different types of neurosyphilis and offer some possible aids to differentiation

TABLE 1 —SPINAL FLUID FORMULAE IN MENINGOVASCULAR AND TABETIC NEUROSYPHILIS

WASSERMANN REACTION	CELLS	TOTAL PROTEIN	GLOBULIN	GOLD SOL.
Positive in 0 05 to 1 cc 40 per cent negative with 0 2 cc Pure vascular neurosyphilis usually negative with 1 cc	Tabes 0 to 200+ Average 25 to 50	17 to 150 mgm per 100 cc Average 78	0 to ++++	0122100000 0134431000 3332100000 4443210000 5555431000
	Meningovascular and acute meningitis 200 to 2000	Average 99 mgm per 100 cc		
	Chronic 0 to 200+	Average 73 mgm per 100 cc		
	Vascular often no increase	Average 50 mgm per 100 cc		

TABLE 2 —VARIETIES OF SPINAL FLUID FORMULAE IN MENINGOVASCULAR NEUROSYPHILIS

WASSERMANN REACTION	CELLS	TOTAL PROTEIN	GLOBULIN	GOLD SOL.	REMARKS
1 Positive 0 6 cc	90	70	++	0244310000	Average
2 Positive 0 4 cc	1200	118	++++	4432100000	Acute meningitis
3 Positive 1 cc	2	45	+	0122100000	Pure vascular
4 Positive 0 05 cc	40	130	+++	5555431000	Paresis sine paresi asymptomatic
5 Positive 1 cc	10	30	+	1233210000	Mild
6 Negative	35	35	+	Negative	Mild meningitis
7 Negative	75	50	++	4443100000	Infrequent

TABLE 3 —VARIATIONS OF SPINAL FLUID FORMULAE IN TABETIC NEUROSYPHILIS

WASSERMANN REACTION	CELLS	TOTAL PROTEIN	GLOBULIN	GOLD SOL.	REMARKS
1 Positive 0 66 cc	25	70	++	0244310000	Average
2 Positive 0 05 cc	75	95	+++	5554421000	Not rare
3 Positive 1 cc	40	30	+	Negative	Relatively inactive
4 Negative	50	50	++	0244310000	Infrequent
5 Positive 0 4 cc	4	25	+	Negative	Infrequent
6 Negative	30	35	+	Negative	Infrequent
7 Negative	3	17	0	Negative	Burned out or stationary

TABLE 4 —SPINAL FLUID FORMULAE IN PARETIC NEUROSYPHILIS

WASSERMANN REACTION	CELLS	TOTAL PROTEIN	GLOBULIN	GOLD SOL.	REMARKS
Positive in 0 05 to 0 2 cc in 95 per cent Slightly weaker reaction rarely found	0 to 200 Average 25 to 50	50 to 150 mgm per 100 cc Average 89	+++	5432100000 5554321000 5555555555	Unusually weak Average Unusually strong

Treatment —Each case of neurosyphilis

weakness of the lower extremities occurs as a result of the pyramidal tracts becoming involved Because of the progressive involve



Fig 186—Section of the spinal cord of the patient shown in Fig 188 with amyotrophic lateral sclerosis showing degeneration of the lateral columns and preservation of the posterior columns The anterior horn cells have disappeared

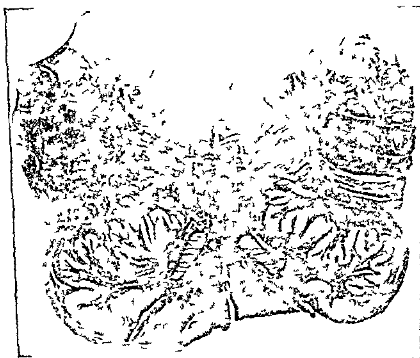


Fig 187—Section of the medulla oblongata from a case of amyotrophic lateral sclerosis shown in Fig 188 The cells of the hypoglossal nuclei are degenerated The pyramidal tracts were not completely degenerated

ment of anterior horn cells in the cervical cord there may be almost constant fibrillary tremors noted in the hand and arm muscles until wasting of these muscles is complete There is no pain no other subjective or objective sensory disturbance and the sphincters are seldom involved In the early stages of the disease the tendon reflexes in the upper extremities may be preserved or even increased but as the wasting of these muscles progresses the reflexes may be dimin

themselves of producing very good results in a substantial percentage of cases In purely vascular neurosyphilis the problem is practically identical with that of vascular syphilis elsewhere in the body and while brilliant results are not attainable the best relief can be obtained by the use of small doses of arsphenamine bismuth and iodides

In the tabetic type of neurosyphilis the problem is very similar to that in general paresis but the results by and large are not quite so satisfactory due largely to the complications that may arise and to the fact that there is often a type of damage that cannot be repaired Some of the mild cases react very satisfactorily to arsphenamine alone Others do very well with a combination of tryparsamide and arsphenamine and not a few react satisfactorily only to fever As a rule it is a matter of slow trial to find the optimum method of treating the tabetic It is in this type of neurosyphilis that the intraspinal injection of the Swift Ellis serum has its greatest place As a matter of fact however it is being used less and less because of the pain and discomfort as well as the risk and technical difficulties inherent in this method

Visceral crises are satisfactorily affected in only about half the cases by whatever method used although in recent times many claim that mechanically produced fevers will give good results in a higher percentage than this Difficulties with the sphincters when once established are only rarely benefited by any form of antiluetic treatment and usually require the care of a genito urinary specialist

Optic atrophy is especially difficult to handle There is considerable divergence of opinion as to the feasibility of handling it at all However there is some evidence that fever does favorably influence some cases especially those that have not developed too far The intracisternal injection of arsphenaminized serum is looked upon favorably by a few authorities Tryparsamide is usually contraindicated in these cases as the drug may injure the optic nerve The chief hazard of tryparsamide is its tendency to damage the optic nerve and visual disturbances occur in 3 to 5 per cent of cases in which it is used though as a rule the damage is slight It must be used however with great care and circumspection in all cases

HARRY C SOLOMON

DISEASES OF THE MOTOR TRACTS

Amyotrophic Lateral Sclerosis —This condition was first adequately described by Charcot in 1865 It is a disease of adult life in which the cervical regions of the spinal cord are first attacked with involvement of the anterior horn cells and the pyramidal tracts As a result of this the muscles of the upper extremities undergo atrophy and present the picture of a lower motor neurone paralysis while a spastic weakness an upper motor neurone syndrome occurs in the lower extremities As the disease progresses upward extension ensues with involvement of the bulbar nuclei and a true bulbar palsy with atrophy of the tongue cheeks facial and pharyngeal muscles is noted in the terminal phase

Etiology —The cause is unknown but it is the writer s opinion that the process may be initiated as a result of ischemia of the cells and tracts at the involved level At the point of the cervical cord enlargement there is a great number of cells with a high respiratory quotient and as diminution of systemic circulatory efficiency occurs these cells may undergo ischemic degeneration The syndrome has been reported in chronic lead poisoning and syphilis Trauma has also been considered a cause

Pathology —The cervical cord is usually the initial site of the lesion Here the anterior horn cells manifest various stages of degeneration and the lateral columns likewise indicate involvement As the process extends upward the cranial nerve nuclei become involved with resulting symptoms of progressive bulbar palsy being added (At post mortem the motor tracts are found degenerated up to the cortex)

Symptoms and Course —The disease usually begins after the third decade of life The first symptom is commonly symmetrical weakness and atrophy of the muscles of the hands The insidious wasting of the thenar hypothenar and interosseous muscles later extends to the shoulders and eventually

Morbid Anatomy—Degeneration of the pyramidal tracts is usually seen in the lower dorsal segments

Symptoms—Slowly progressive weakness of both lower extremities is the characteristic symptom The weakness is bilateral and of a spastic type In this disorder an extreme scissors gait' may be seen as a result of the extreme rigidity of the adductor muscles Increased tendon reflexes positive Babinski and ankle clonus are almost invariably present but sensory changes are absent The sphincters are rarely involved and the upper extremities are not affected Mills reported a case in which the disease appeared to be unilateral

Diagnosis—With evidence of a progressive bilateral pyramidal tract involvement to the state of a spastic paraplegia the disease should be suspected if there is no evidence of any involvement of other structures—especially if the spasticity seems to be greater than the degree of weakness *Multiple sclerosis posterolateral sclerosis syphilis* and *spinal cord tumor* may resemble the disease but in all of these there are symptoms of involvement of other structures

Treatment—Where an etiology can be established the treatment is logically the treatment of the basic disease In the absence of a determined etiology vitamin therapy should be initiated

Prognosis—The prognosis is poor unless the cause is discovered and successfully treated before the changes are irreversible

Progressive Bulbar Palsy (*Progressive Glosso pharyngo labial Paralysis*) —*Definition*—This is an uncommon disease of later life in which symptoms of a lower motor neurone type of paralysis involving the muscles of phonation mastication and deglutition occur with atrophy of the muscles of the tongue lips jaws larynx and pharynx

Etiology—No cause is known but it is possible that an ischemic type of cell death occurs because of inadequacy of circulation in the pons and medulla The syndrome may be added to that of amyotrophic lateral sclerosis as a terminal phase

Symptoms and Course—The disorder usually begins around fifty years of age The earliest symptoms are difficulty in articulating the lingual and labial sounds and interference with chewing because of the weakness of the tongue and muscles of mastication Atrophy of the involved muscles progresses and the presence of fibrillary tremors in the muscles of the pharynx tongue masseters and cheeks is a prominent feature and is presumably due to involvement of the cells in the cranial nerve nuclei When atrophy of a muscle becomes complete the tremors cease The disease progresses at a variable rate and sometimes may appear to be arrested As a rule however, the disease terminates fatally in from six months to three years Death usually occurs from aspiration pneumonia or from inanition The difficulty in swallowing may be slow in appearing Solid foods or liquids of low specific gravity may at first present difficulty while soft foods milk cream and thin broths may be swallowed with comparative ease No sensory disturbance occurs and in typical cases no loss of power of the extremities is seen Intelligence is likewise preserved

Diagnosis—The disease offers few diagnostic difficulties if it is kept in mind that atrophy of the facioglossopharyngolabial muscles is a distinct feature and that there are no associated disturbances of sensation or power elsewhere In *pseudobulbar palsy* similar difficulties of speech mastication and deglutition may occur but there is no muscle atrophy In *myasthenia gravis* the symptoms fluctuate are either produced or aggravated by effort and are relieved by rest In uncomplicated myasthenia there is no atrophy of the tongue or other muscles In *amyotrophic lateral sclerosis* which may produce a bulbar palsy there is evidence of cervical spinal cord and pyramidal tract disease In *tumors* and other intrinsic lesions of the brain stem sensory and other motor symptoms are present

Treatment—No successful treatment is known but sustaining life by soft diet and vitamin reinforcement is advisable If there is evidence of circulatory inadequacy circulatory stimulants and transcerebral diathermy may be helpful

Progressive Spinal Muscular Atrophy (*Aran Duchenne Progressive Muscular Atrophy Chronic Anterior Poliomyelitis*) —This is characterized by progressive muscular wasting due to degeneration of anterior horn cells of the spinal cord It usually

ished or abolished while in the legs the tendon reflexes may at first be normal but as the lesion advances they eventually become increased and pathological plantar reflexes are demonstrable Within six to eight months a complete flaccid paralysis of the arms may become established and spastic paralysis of the lower extremities results in total disability of the individual The terminal phase of the disease is ushered in with the involvement of bulbar cranial nerve nuclei, with resulting difficulty in swallowing (dysphagia), chewing and talking (dysarthria) Death may occur from deglutition death usually occurring within three to ten years of onset

Treatment —No form of treatment is uniformly successful, much benefit has been reported from the administration of large doses of vitamin B_6 (8 cc of wheat germ oil and 50 mg or more of alpha tocopheral acetate daily) by some investigators, but others, including the author have seen no beneficial results Laminectomy and decompression have advocates as has deep x ray therapy During the stage of bulbar paralysis care must be exercised to prevent choking and a soft diet must be provided



Fig 188 —Amyotrophic lateral sclerosis of three years duration showing muscular atrophy of hands and upper limbs Patient died of bulbar symptoms one month after this photograph was taken Sections of the spinal cord and medulla oblongata of this case are shown in Figs 186 and 187

pneumonia or choking The sensory tracts are not involved and intelligence remains intact but occasionally involuntary crying and laughing occur

Differential Diagnosis —The picture resembles *syringomyelia* but subjective or objective sensory involvement is absent and the course is much more rapid than in syringomyelia A tumor implicating the *cervical spinal cord* may present a similar picture but again sensory changes are nearly always present *Progressive spinal muscular atrophy* does not involve the pyramidal tracts.

Prognosis —The prognosis is grave with

Primary Lateral Sclerosis (*Spastic Spinal Sclerosis of Erb*) —The group of symptoms described under this name by Erb in 1875 is regarded as a syndrome of variable etiology The symptoms are progressive spastic paralysis of the lower extremities with the typical reflex changes of bilateral pyramidal tract involvement.

Etiology —The etiology is obscure but many cases are undoubtedly due to vitamin deficiency The writer believes that many are due to demyelinization as a result of chronic passive congestion of the cord in patients with disorders effecting an increase of intrathoraco abdominal pressure

Diagnosis.—Because of the familial tendencies and the implication of the proximal portions of the limbs the greatest difficulty may be experienced in differentiating this condition from *progressive muscular dystrophy* but the absence of hypertrophy and pseudohypertrophy and the presence of fibrillary tremors of the muscles serve to distinguish it. *Congenital myatonia* differs from it in being congenital in origin and without familial tendencies and by the proportionately greater involvement of the muscles of the trunk at a much earlier age but pathologically the two conditions cannot be separated It should not be confused with a form of *primary* or *idiopathic wasting* that occurs in very young babies because of failure of nutrition

Prognosis.—As in the adult form the disease generally ends fatally as the result of intercurrent disease Recovery is unknown

The Neural Form of Progressive Muscular Atrophy (*Charcot Marie Tooth Type Peroneal Atrophy*).—*Definition*.—This type of progressive muscular atrophy was described independently by Charcot and Marie and by Tooth in 1886 It is essentially a slowly progressive atrophy of the peroneal muscles

Etiology.—The exact cause is unknown but there is a marked heredofamilial tendency and a congenital defect is likely Isolated cases are also seen

Pathology.—The predominant lesions are found in the nerves and both the anterior and posterior roots may show degenerative changes The cord is also involved and degeneration may be noted in the posterior and lateral columns The anterior horns are seldom intensely affected but may show minor changes

Symptoms and Course.—Onset is usually in childhood or before puberty but may occur in early adult life Atrophy and pes varus and equinovarus or other deformities of the foot occur insidiously with resulting difficulty in walking Ankylosis of the ankle and of intrinsic joints of the foot may develop Slowly the atrophic changes spread to involve the muscles below the knee—only rarely do the muscles above the knee become involved Eventually the muscles of the hands and forearm become similarly affected with no involvement about the elbows It is noteworthy that the atrophy is out of proportion to the loss of power A wizened leg or hand may carry on to a surprising degree Fibrillary tremors are common and reflexes are lost in the involved muscles Sensation is usually disturbed along the same neural pattern but progresses even more slowly than the motor disturbance



Fig 189.—Progressive neural muscular atrophy (progressive muscular atrophy of the Charcot Marie-Tooth type) of about twenty years duration showing atrophy most intense in the distal portions of the extremities

Subjective sensory symptoms such as paresthesias and pain are fairly common and occasionally trophic changes of the skin occur especially in the feet

Diagnosis.—An old *peripheral neuritis* may present a picture resembling the disease but there the onset occurs with greater rapidity and is usually painful

Prognosis.—Life may be extended to old

begins with atrophy of the small muscles of the hands but the shoulder or other muscles may become involved first The disease generally shows symmetrical involvement but it may originate and remain as a unilateral process for some time

Etiology—Occasionally the symptom complex is caused by *syphilis* and may respond dramatically to antiluetic treatment but as a rule the cause cannot be determined In some instances it has followed years after an attack of acute poliomyelitis The disease like others in this group termed abiotrophies by Gowers occurs in middle life and the author thinks that the process is due to ischemia of the anterior horn cells The thought is that these large cells having a high nutrition requirement begin to degenerate when circulatory inadequacy occurs in later life

Morbid Anatomy—The characteristic lesions consist of atrophic and degenerative changes of the anterior horn cells In typical cases no inflammatory changes are noted

Symptoms—Muscular wasting and resulting weakness begin insidiously and slowly progress through the various levels of the spinal cord Usually the hands are involved first the forearms arms shoulders trunk and lower extremities later Fibrillary tremors are frequently noted in the muscles involved The disease is a slowly progressive rather than a malignant one and it may be fifteen to twenty years from the time of onset before it is a distinctly disabling one As atrophy involves a muscle its reflex may be abolished but the reflexes at uninvolved levels of the cord remain normal since the pyramidal tract is not implicated No sensory changes occur

Diagnosis—*Amyotrophic lateral sclerosis* is a more rapidly progressive disease and the pyramidal tracts are always involved *Syringomyelia* presents the typical dissociation of pain sensation as well as pyramidal tract signs

Prognosis—Life may be lived in comparative comfort for many years and death usually occurs from intercurrent disorders Remissions often take place with the disease becoming stationary

Treatment—General tonic and supportive measures with vitamin reinforcement of the diet appear to retard the progress of the disease and may effect a remission

Progressive Spinal Muscular Atrophy of Childhood of Familial or Hereditary Character (*Werdnig Hoffmann Type*)—*Definition*—Progressive spinal muscular atrophy of childhood is a condition first described by Werdnig and later by Hoffmann, which differs from the adult form of spinal atrophy in its hereditary and familial tendencies It develops in the early years of life involving first the muscles of the pelvic girdle then extending toward the ends of the limbs It is dependent on degeneration of the anterior horn cells and the peripheral motor nerve fibers and on alterations in the crossed pyramidal tracts

Etiology—The cause is unknown Several children of the same parents may be affected but isolated cases also occur The condition is most probably dependent upon a defect in the development of the nervous system (abiotrophy)

Morbid Anatomy—In Hoffmann s patients there was degeneration of the multipolar cells of the anterior horns of the spinal cord intense degeneration of the anterior roots and less marked change in the peripheral nerves together with degeneration of the crossed and direct pyramidal tracts The muscles undergo simple atrophy

Symptoms and Course—The disease begins in childhood and progresses slowly The child either never learns to walk or loses the ability to do so The condition is manifested by weakness and atrophy of the muscles of the trunk and pelvic girdle the iliopsoas quadriceps femoris and later of those of the upper limbs and neck The proximal portions of the limbs are affected first the changes then slowly extending to the hands and legs A year or more elapses before the distal portions of the limbs are involved The wasting of the muscles is generally symmetrical and so uniform is the atrophy that in the beginning it may be concealed by fatty tissue The tendon reflexes are abolished Fibrillary tremors may be present but frequently are absent. Hypertrophy never occurs Sensation is not disturbed Bulbar symptoms sometimes develop but are rare The disease is progressive and generally ends fatally before the seventh year

the cerebrospinal fluid from its point of formation in the choroid plexuses of the lateral and third ventricles to the fourth ventricle and thence to the subarachnoid space through the foramina of Magendie and Luschka When normal absorption of the fluid in the subarachnoid space is thus prevented its accumulation in the lateral and third ventricles produces *internal hydrocephalus (obstructive internal hydrocephalus)*

The *diagnostic test* for this is injection of a neutral dye (indigo carmine) which is specially prepared into one of the lateral ventricles and a few minutes later removal of some of the spinal fluid by lumbar puncture If the dye does not appear in the fluid thus obtained there is obstruction in the sylvian aqueduct or in the foramen of Monro By introducing air into the lateral ventricle (Dandy s ventriculography) the exact site of the obstruction can often be determined The *prognosis* of congenital hydrocephalus is serious although in many children the disease is arrested and physical and mental development is more or less normal Measurement of the skull at regular intervals enables the physician to determine how rapidly the condition progresses

Treatment is hazardous but recoveries have been observed in Bellevue Hospital after opening the wall of the third ventricle Removal of fluid from the ventricles is easy before the fontanels have closed but is of little if any benefit it is not without danger of sudden collapse if performed too rapidly Dandy and others have actually put sounds and later tubes through partially obstructed sylvian aqueducts with good results in a few cases This is of course a difficult and dangerous operation

Meningocele is hernia of the membranes of the brain through a cleft in the skull *encephalocele* is also protrusion of the brain substance usually in the occipital region in the median line

Spina bifida is a congenital defect of the sacral or lower lumbar vertebrae which is very often associated with protrusion of the meninges These form a lump under the skin which is soft and contains cerebrospinal fluid and at times portions of the cauda equina or of the spinal cord itself Spina bifida is apt to be associated with other developmental anomalies such as cervical rib syringomyelia or hydrocephaly Sometimes when the bony defect is slight there is no lump (meningocele) but a tuft of hair or a pad of fat lies over the lesion this condition is called *spina bifida occulta* Both *spina bifida* and *spina bifida occulta* may produce a definite syndrome The lower limbs are weak and often much atrophied below the knee There is incontinence of urine or perhaps enuresis Trophic ulcers are very prone to develop on the soles of the feet either spontaneously or as a result of slight injury to the skin (a blister for example produced by a badly fitted shoe) The ankle jerks are absent as a rule This condition may manifest itself only at puberty when the more rapid growth of the spine compared with the spinal cord and roots within causes pernicious traction on the cauda equina which results in functional disturbance of the sacral and lower lumbar motor and sensory roots

The *prognosis* depends on the extent of the hernia and what it contains The sac if large may rupture and cause death at once or later from purulent meningitis Surgical intervention has saved some patients. If the sac contains only fluid and meninges the chance of cure is greater than when it also contains nerve structures

Treatment —The best time for the operative treatment of spina bifida is usually the first few weeks of life Operation very soon after birth is indicated in some cases when the sac ruptures or threatens to rupture Penfield and Cone have recently devised a new technic for the prevention of hydrocephalus following operation on spina bifida

Defects of the Spinal Cord —Entire absence of the spinal cord (*amyelia*) is associated with anencephaly *Amyelencephaly* is absence of both brain and spinal cord *Atelomyelia* is lack of development of the cord *e g* absence of the pyramidal tracts *Asymmetry* of the cord occurs with possibly defective development of one pyramidal tract In *heterotopia* the gray portions of the cord are displaced so that patches of gray matter are scattered among the bundles of white fibers this condition is sometimes produced artificially at autopsy by rough removal of the cord *Micromyelia* the presence of an abnormally small spinal cord is

age but there is no known successful treatment that can be expected to alter the course of the disease Remissions or arrests may occur before full evolution of the disease picture

Treatment —Some successes are reported with vitamin B and E therapy but are difficult to evaluate because of the tendency for arrest to occur at various stages

SAMUEL B HADDEN

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HEREDITARY AND FAMILIAL DISEASES OF THE NERVOUS SYSTEM

THE nervous system like the other structures of the human body is not always complete or normal at birth Furthermore it may appear to be normal at birth and for a number of years thereafter then suddenly or gradually there develops some defect in function or structure which manifests itself as a syndrome or disease The more important of these disturbances including those which occur in more than one member of a family are briefly described here

MALFORMATIONS OF THE BRAIN MENINGES AND SPINAL CORD

At birth the brain may be entirely absent—*anencephalia*—or absent except for the cerebellum and part of the basal ganglia Such conditions are associated with *acrania* Sometimes when development is arrested the cerebrum remains single instead of separating into two hemispheres there is only one ventricle and the rudiments of the eyes unite to form one eye (*cyclopia*) When the skull is abnormally small (*microcephaly*) and the brain is also very small and defectively developed the condition is known as *micrencephaly* Greater development of one side of the brain than of the other is called *asymmetry* In *porencephalus* a cyst is connected with the ventricle and there is lack of cerebral substance In *nuclear aplasia* certain cranial nerve nuclei are absent or imperfectly developed When the oculomotor nuclei are aplastic ptosis of the upper eyelids and weakness or absence of movement in the eyeball ensue This condition may be present at birth or develop slowly and progressively in adult life producing bilateral ptosis paresis of the extra ocular muscles and later paresis of the internal muscles of the eye It is not always associated with other involvement of the central nervous system and when it occurs alone is probably due to a congenital imperfection of the nerve cells of the oculomotor nuclei which was not apparent at birth

Hydrocephaly, sometimes present at birth is characterized by abnormal enlargement of the head and dilatation of the ventricles of the brain at the expense of the brain substance which as a rule is flattened into thin sheets surrounding the ventricles It is usually internal and bilateral but occasionally the ventricular distention is restricted to one lateral ventricle as the result of either a developmental anomaly of the brain or of some lesion in the ventricular walls *External hydrocephaly* is a condition characterized by accumulation of fluid in the distended subarachnoid space over the surface of the brain and by atrophy or shrinking of the brain substance Moderate hydrocephalus is not incompatible with normal intelligence and may even be associated with brilliance Generally however it is associated with some degree of mental impairment and often also with weakness of the limbs because the pyramidal tracts are degenerated or ill developed.

The congenital form is frequently caused by total or partial obstruction of the aqueduct of Sylvius this prevents circulation of

the cerebrospinal fluid from its point of formation in the choroid plexuses of the lateral and third ventricles to the fourth ventricle and thence to the subarachnoid space through the foramina of Magendie and Luschka When normal absorption of the fluid in the subarachnoid space is thus prevented its accumulation in the lateral and third ventricles produces *internal hydrocephalus* (*obstructive internal hydrocephalus*)

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associated with such conditions as Friedreich's disease A spinal cord is seldom completely double (*diplomyelia*) and may be so in only a few segments The condition is due to failure of the central canal of the cord to close or contract normally This duplication of the canal is not so rare as some of the other anomalies

Types of Mental Deficiency —Mental deficiency is of many degrees and grades In some patients there are obvious organic defects of the brain (microcephaly or hydrocephaly for example) while in others the brain appears to be normal even on microscopic examination

The Profound Idiot —This is the lowest type of mental defective He is usually of small size physically abnormal and at any age more helpless than the normal infant He has apparently no mentality

The Superficial Idiot —Slightly higher in the scale but still in the idiot class is the superficial idiot Such individuals may be able to speak very imperfectly can walk and perform other muscular movements with better coordination than can the profound idiot They are often mischievous ill tempered and difficult to manage

The Idio imbecile and the Imbecile —The third grade is the idio imbecile and the fourth the imbecile which includes three grades—low middle and high Imbeciles can be trained in the various arts and trades but require a long apprenticeship and a good deal of supervision preferably in a colony

The Moral Imbecile —This type is not only mentally but morally deficient and needs constant supervision He can like other imbeciles be trained but must be carefully watched because of his tendency to do evil things

Backward Children —The very large class of backward children can be trained to fill a place in the outside world since their mental processes are normal but slower than the average Some of these individuals appear perfectly normal except during excitement illness or under other adverse conditions

Amaurotic Family Idiocy —A type of idiocy with peculiar pathology is the so called amaurotic family idiocy (Tay Sachs disease) which occurs almost exclusively in Jewish children and is fatal within two years or a little more It is associated with optic atrophy and blindness and the appearance of a cherry red spot at the macula in each retina The nerve cells throughout the brain and spinal cord undergo characteristic degeneration becoming greatly enlarged (ballooned) and the Nissl substance becomes fragmented and collects about the eccentric nucleus The neurofibrils are pushed to the periphery of the cell body This form of idiocy may affect several children in one family

In addition to this now well known type of the disease there is a late infantile type (Jansky Schob and Bielchowsky) and a juvenile type described by Spielmeyer and Vogt The late infantile form begins at about three and one half years of age and may run a course of four years The juvenile type begins later in life between seven and eight years of age and lasts longer It is found most often in Gentile children and the cherry red spot at the macula is often absent In 1928 it was discovered that the pathologic changes in the brain of amaurotic family idiocy might be part of a larger syndrome called Niemann Pick's disease which is a disturbance of the phospholipid metabolism

Gargoylism —Gargoylism is a heredofamilial disease which has recently attracted the attention of pediatricians and neurologists The changes in the nervous system resemble somewhat those found in amaurotic family idiocy although the mental defect is not nearly so great and there is no optic atrophy as a rule There is some defect in vision due to a lipoid like deposit in the cornea

The disease begins to be evident in some cases in the first few months of life—the features are peculiar and the bones do not develop normally As the child grows older the prominent characters of the disease become more noticeable—the child resembles somewhat an achondroplastic dwarf with short arms and legs and some kyphosis The head is large there are a saddle nose and coarse lips the eyebrows are bushy and the neck is short the abdomen is large and there is often an umbilical hernia genu valgum is present the liver and spleen are enlarged The mental defect varies in different cases apparently depending upon the number of cells affected in the cerebral cortex *Only*

a few cases have come to autopsy In one case recently examined the brain was large and very heavy with a slight hydrocephalus The *leptomeninges* were much thickened over the frontal lobes The *convolutions* were large and the sulci wide The sella turcica was lengthened anteroposteriorly

Sections of the brain and spinal cord showed many cells much enlarged and rounded with an eccentric nucleus and no normal tigroid substance

The *disease is not necessarily fatal* and these patients are quite *active and able to* play about.

Mental Deficiency and Epilepsy—At times mental deficiency and epilepsy are associated Epilepsy occurs in some cases in more than one member of a family

Tuberous Sclerosis—Tuberous sclerosis is a congenital *developmental anomaly of the* brain associated clinically with epilepsy as a rule and with some conduct disorder very often. It is characterized by enlarged convolutions which feel hard like marbles in the fresh brain The lining of the lateral ventricles has hard white *projections* in places resembling candle drippings Microscopic study of affected brain areas shows giant astrocytes and peculiarly developed nerve cells with many thick processes

The changes in the nervous system are usually *associated* with adenoma sebaceum over the nose and cheeks and *usually with* neurofibromatosis of the skin *Cafe au lait* spots and nevi are also present in the skin of some patients Often associated with these changes are rhabdomyoma of the heart and fibrous *nodules* on the serous coat of the intestine and *sometimes on the surface* of the kidney There may be skeletal changes such as fusion of two vertebrae etc In rare instances a peculiar tumor 'mulberry tumor' or phacoma of the retina can be seen with the *ophthalmoscope*

The condition may be well developed in the brain at birth and may even be associated with tumor formation in the brain This tumor is usually classified as spongioblastoma multiforme and in one case in our series there was a spongioblastoma polare. The x ray appearance *of the skull is* sometimes characteristic—small white apparently calcified nodules can be seen scattered throughout the brain Probably many cases of idiopathic epilepsy have tuberous sclerosis as their pathologic basis

Many cases resist the usual treament for epilepsy and because of their conduct disorders *must* be committed to an institution These patients *are often sullen* and danger ous and even criminal in their conduct

LEWIS STEVENSON

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LITTLE'S DISEASE

(Congenital Spastic Stiffness of the Limbs)

The one well known disease *of the* pyramidal tracts which is associated with little or no mental defect is Little s disease This is congenital or infantile in origin and results *from lack* of development (*agenesis*) of the *pyramidal tracts which* leads to atrophy or sclerosis of the lateral *columns of the spinal* cord The condition is sometimes seen in twins The symptom complex can no doubt be produced by a number of conditions which operate before or at the time of birth but *its most* important cause is premature birth *Meningeal hemorrhage* and congenital syphilis are responsible *for some* cases and trauma to the head during difficult labor even without visible hemorrhage of the brain may arrest development of the *pyramidal tracts* The symptoms can be observed usually within a year of birth but may at times not appear *for a number of* years Patients begin to walk very late and manifest the well known cross legged *progression* due to spastic adduction of the thighs The *arms are less* involved The deep reflexes are *exaggerated especially* at the knee and ankle and there is often a *double*

Babinski sign When the condition is mild it responds slowly to massage and any necessary orthopedic therapy, such as tenotomy Some of the posterior roots of the spinal nerves supplying the spastic muscles have been resected at times with favorable results If the condition is severe the patient gradually becomes more and more helpless as the size and weight increase Death often results from intercurrent disease before he reaches twenty years of age

Hereditary Hemiplegia —This is a rare form of hereditary hemiplegia which is sometimes associated with atrophy of the paralyzed side

Hereditary Spastic Spinal Paralysis is a rare disease which affects several members in many generations of one family It causes slowly progressive paralysis of the legs which begins at about the age of five and continues twenty or thirty years

LEWIS STEVENSON

HEREDITARY SPINAL ATAXIA

(*Friedreich s Disease*)

A common disease which begins between the ages of six and fifteen years and may affect several brothers and sisters is hereditary spinal ataxia The lesion involves the posterior columns and pyramidal tracts of the spinal cord and there is some degeneration in the direct cerebellar tracts and cerebellum These changes lead to ataxia weakness in the legs pes cavus, scoliosis sometimes manus cava and occasionally to nystagmus and tremor of the head Two or more children of one family may have the scoliosis and characteristic deformity of the feet while one or more may manifest the complete syndrome which includes not only evidences of tract degeneration in the spinal cord but also well marked signs of cerebellar disturbance such as nystagmus nodding of the head syllabic speech and asynergy of both arms and legs The bilateral deformity of the foot is striking the dorsum is high the arch deeply hollowed and the great toe hyperextended at the metatarsophalangeal joint and flexed at the phalangeal joint There is a kind of 'permanent Babinski sign' The ankle jerks are absent and also the knee jerks The deep reflexes in the arms may be lost in the late stages of the disease Occasionally in well marked cases the palms of the hands are hollowed just like the soles of the feet, and the fingers are hypotonic and become hyperextended when the arms are held straight out in front with the palms down The bladder and rectal sphincters are not involved and there is no pain or loss of superficial sensation At times when the cerebellar signs are more marked than those referable to the spinal cord the condition may resemble Marie's hereditary cerebellar ataxia

Hereditary cerebellar ataxia, which is allied to Friedreich s disease, develops somewhat later in life and causes more degeneration in the cerebellum than in the spinal cord Many of these hereditary defects in the structure of the nervous system (*abiotrophies*) are not true to type, but merge one into the other as these two diseases quite commonly do

LEWIS STEVENSON

FAMILY PERIODIC PARALYSIS

This is a rare hereditary disease which begins in early life and lasts for many years The paralysis comes on very often during the night and is a flaccid palsy of legs trunk and arms without sensory disturbance or involvement of the cranial nerves It lasts for between a few hours and a few days and is associated at times with some dilatation of the heart

LEWIS STEVENSON

HEREDITARY CHOREA

(*Huntington s Chorea*)

This disease begins in middle life and affects several generations as well as more than one member of a single generation It is progressive and degenerative in type and is associated with gradual progressive dementia The disease is easily recognized by the jerky irregular movements of the entire body The gait is very much disturbed The head is twisted about from side to side and the shoulders are raised on one side and then on the other with irregular, jerky twisting movements of the hands and arms as the

patient walks rather hurriedly across the room. All movements seem to be exaggerated or overdone and there is much grimacing The patient can by an effort of the will control these movements for a minute or two but they soon begin again, and like other involuntary movements increase when the patient knows he is under observation Men and women are about equally affected Heredity is the chief etiologic factor rheumatism and other infections play no part as they do in the chorea of Sydenham The lesion is a degenerative change in certain brain cells The small motor cells of the caudate nucleus and the putamen are particularly affected by atrophy Some of the pyramidal cells in the psychomotor areas are also involved—a fact which no doubt accounts for the gradual development of dementia The choreic movements probably result from atrophy of the cells in the corpus striatum Sometimes there is a good deal of proliferation of the glia in the brain, and at times there are vascular changes suggestive of encephalitis Although the condition becomes gradually worse some improvement may occasionally be brought about by administration of such sedatives as bromides luminal or hyoscine and a course of tonic treatment.

There is a type of hereditary chorea without dementia which begins earlier in life than Huntington s type—often at the age of puberty It affects the muscles of the face and arms but leaves the legs unaffected Patients with this disease may lead a fairly normal active life

LEWIS STEVENSON

WILSON S DISEASE

(*Progressive Lenticular Degeneration*)

This is a familial somewhat rare condition It affects young people and is associated with a peculiar hobnail cirrhosis of the liver The clinical manifestations are bilateral athetoid movements of the hands arms legs, and face The face usually bears a grin which spasmodically breaks into a laugh since there is considerable emotional disturbance The athetoid twistings are rhythmic and increase on voluntary movement The limbs are more or less spastic and contractures eventually develop The deep reflexes are active but there is no Babinski sign because the pyramidal tracts are not affected There is no actual weakness of the muscles or loss of sensation The abdominal reflexes are preserved The speech is dysarthric and there is difficulty in swallowing The disease is progressive and fatal within a few years Postmortem examination of the brain reveals extensive changes in the lenticular nuclei sometimes cavity formation.

LEWIS STEVENSON

APLASIA AXIALIS EXTRACORTICALIS CONGENITA

(*Pelizaeus Merzbacher Disease*)

This is a rare congenital and familial disease which begins in infancy makes rapid progress at first and later follows a more chronic course It somewhat resembles multiple sclerosis The chief clinical features of the disease are slowness of speech fixation of facial expression nystagmus ataxia with spasticity of the legs and mental deficiency The lesion is an atrophy of the white matter of the brain

LEWIS STEVENSON

HEREDITARY PROGRESSIVE SPINAL AND NEURITIC MUSCULAR ATROPHIES

There are three types of hereditary progressive spinal and neuritic muscular atrophy the infantile form of Werdnig Hoffmann which begins in the first or second year of life and causes weakness and atrophy of the muscles of the buttocks back and legs and later of the muscles of the shoulders and neck with final involvement of other muscles the adult form (Dana) which is rapidly fatal and begins at about the age of thirty or fifty years the Charcot Marie Tooth form in which the muscles of the legs (peronei muscles) and later of the forearms atrophy

LEWIS STEVENSON

HEREDITARY PROGRESSIVE DYSTROPHIES

In the group of hereditary progressive dystrophies of the muscles and the nerves supplying them are included a number of conditions

Pseudohypertrophic muscular dystrophy is perhaps the best known It may affect several children in a family without any history of ancestral nervous or muscular disease It occurs in boys much more often than in girls At times the disease is inherited through several generations It usually begins in childhood The patient develops a waddling gait falls easily and finds difficulty in climbing stairs He cannot rise from the ground without the use of his arms and cannot stand erect until he has climbed up his legs with his hands Hypertrophy of the calf muscles becomes marked and the muscle is hard and unnatural to the touch The infraspinatus supraspinatus and deltoid as well as certain other muscles may also undergo hypertrophy Lordosis develops The child gradually becomes more helpless and the pseudohypertrophy may give place to atrophy of the muscles

Juvenile Form of Progressive Muscular Dystrophy (Erb s Type) —In juvenile progressive muscular dystrophy the muscles of the shoulder girdle are first affected There is hypertrophy of some muscles of the shoulder girdle and also at times of some of those of the pelvic girdle The thighs deep muscles of the back and of the upper arm become atrophic Later atrophy takes place in the hypertrophied muscles The face forearm hand and leg muscles remain normal for a long time The disease begins in childhood or a little later It is one of the rarest forms of dystrophy and like other primary myopathies gives evidence of no change in the central nervous system

Landouzy Dejerine Dystrophy —In the Landouzy Dejerine type of dystrophy there is no muscular hypertrophy but marked atrophy of the muscles of the face shoulder girdle and arm Those of the forearm hand and legs and the deep muscles of the back as a rule remain normal The facial atrophy usually begins early in life and produces a peculiar expression called the *myopathic facies* The lips appear thickened and the lower lip curves downward (*bouche de tapir*) because of the atrophy in the orbicular muscle of the mouth The ocular muscles and those of deglutition are not affected The patient later develops a marked lordosis the peculiar posture and awkward gait give the impression of a pouter pigeon

Sometimes forms of muscular dystrophy seem not to remain true to type and in certain cases characteristic signs of at least two of these types have been seen in one individual

LEWIS STEVENSON

MYOTONIA CONGENITA

(*Thomsen s Disease*)

This is a disease which usually affects several members of the same family and is transmitted from generation to generation The muscles are so affected that at the beginning of a muscular movement it is extremely difficult to overcome a certain muscular stiffness (hypertonus) After several contractions the muscle limbers up,' but this disappears as soon as the muscle is at rest again The disease begins very early in life and is chronic It has been demonstrated at Bellevue Hospital and amply confirmed elsewhere that quinine hydrochloride 5 or 10 grains two or three times daily acts specifically in the removal of myotonic symptoms in this disease probably by chemical reaction on the neuromuscular junction

LEWIS STEVENSON

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MYATONIA CONGENITA

(*Oppenheim s Disease Amyotonia Congenita*)

This is a rare disease in infants which was described by Oppenheim in 1900 Clinically it is the very opposite condition to myotonia congenita The two terms are often confused During the first few months of its life the child seems paralyzed—the muscles are flabby and atonic and the deep reflexes are absent or very sluggish The legs are most severely affected but the trunk and arms are also involved The arms and legs hang loosely and the child cannot move them to any great extent The muscles do not atrophy or at least do not appear to The

disease is congenital and does not usually occur in more than one member of a family Thirty per cent of patients die within the first year The pathology of the condition is not fully understood Some believe the disease to be a fetal form of poliomyelitis In one case recently studied at autopsy the lower part of the spinal cord showed marked changes in the anterior horns. The cells were reduced in number and those remaining were atrophic There was much fat in the anterior horns and fat in the radicles of the anterior roots running from the anterior horn cells to the margin of the cord This represented broken down myelin sheaths When stained with silver carbonate there was a very marked gliosis seen in the anterior horns The changes in the upper regions of the cord were much less pronounced Anatomically there seems to be no difference between Oppenheim s disease and Werdnig Hoffmann paralysis Oppenheim states that some patients have improved and he considers the condition to be one of delayed development of the muscles

MYOTONIA ATROPHICA

This is a rare disease which begins between the ages of twenty and thirty years and is characterized by peculiar myotonic stiffness of the muscles as well as by atrophy of special muscle groups *i.e* the orbicular muscles of the eyes and mouth (tapir mouth and myasthenic facies) the sternomastoids extensors of the arms supinator longus and the vasti muscles of the thigh Other features are increased lacrimation and salivation a peculiar defect in articulation and general emaciation The condition is most peculiarly associated with cataract of the eye several members of one family as well as the patient with atrophic myotonia may suffer from cataract

LEWIS STEVENSON

TERATOMAS TERATOID AND DERMOID TUMORS GLIOMA RETINAE

Certain tumors of the brain and of the spinal cord which are present at birth may become manifest almost at once or at times not until much later in life **Hypophysial** dermoids are found at the base of the skull in the sella turcica near the olfactory lobes or at the optic chiasm Other intracranial dermoids are found between the medulla and pons and elsewhere. Sometimes they grow from the dura mater, often in the median line in the tentorium cerebelli **Cholesteatoma** may occur in the bones of the skull or within the brain substance or ventricles **Glioma of the retina** is congenital, and is reported to have occurred in several children of a single family

LEWIS STEVENSON

CONGENITAL SYPHILIS

Congenital syphilis of the nervous system is not uncommon It gives rise to syphilitic meningitis and to juvenile paresis or tabo paresis. A child with congenital lues may very soon after birth have basilar luetic meningitis with secondary hydrocephalus and yellow spinal fluid (xanthochromia) or may develop normally until the age of five or ten years and then shows symptoms of general paresis The mentality drops the memory becomes poor and dementia sets in Epileptic fits may occur as in older paretics The deep reflexes at the ankle and knees are often absent (taboparesis) and the pupils are sometimes sluggish to light

LEWIS STEVENSON

MYASTHENIA GRAVIS

Myasthenia gravis is a disease of the muscles particularly those of the face the masseters and the muscles for deglutition and speaking which makes them fatigue very quickly The facies is nearly always characteristic with ptosis of one or both upper eyelids The generally sad expression is almost pathognomonic of this condition

Incidence —The disease occurs in adults as a rule but occasionally it is seen even in a malignant form in young people

Etiology —The cause of myasthenia gravis is not known The observation of a persistent thymus in the form of a thin sheet in some patients at autopsy and the fact that symptoms of the disease often disappear during pregnancy arouse suspicion of some endocrine defect.

Pseudohypertrophic muscular dystrophy is perhaps, the best known It may affect several children in a family without any history of ancestral nervous or muscular disease It occurs in boys much more often than in girls At times the disease is inherited through several generations It usually begins in childhood The patient develops a waddling gait falls easily and finds difficulty in climbing stairs He cannot rise from the ground without the use of his arms and cannot stand erect until he has 'climbed up his legs with his hands Hypertrophy of the calf muscles becomes marked and the muscle is hard and unnatural to the touch The infraspinatus supraspinatus and deltoid as well as certain other muscles may also undergo hypertrophy Lordosis develops The child gradually becomes more helpless and the pseudohypertrophy may give place to atrophy of the muscles

Juvenile Form of Progressive Muscular Dystrophy (Erb s Type) —In juvenile progressive muscular dystrophy the muscles of the shoulder girdle are first affected There is hypertrophy of some muscles of the shoulder girdle and also at times of some of those of the pelvic girdle The thighs deep muscles of the back and of the upper arm become atrophic Later atrophy takes place in the hypertrophied muscles The face forearm hand and leg muscles remain normal for a long time The disease begins in childhood or a little later It is one of the rarest forms of dystrophy and like other primary myopathies gives evidence of no change in the central nervous system

Landouzy Dejerine Dystrophy —In the Landouzy Dejerine type of dystrophy there *is no* muscular hypertrophy but marked atrophy of the muscles of the face shoulder girdle and arm. Those of the forearm hand and legs and the deep muscles of the back as a rule remain normal The facial atrophy usually begins early in life and produces a peculiar expression called the *myopathic facies* The lips appear thickened and the lower lip curves downward (*bouche de tapir*) because of the atrophy in the orbicular muscle of the mouth The ocular muscles and those of deglutition are not affected The patient later develops a marked lordosis the peculiar posture and awkward gait give the impression of a pouter pigeon

Sometimes forms of muscular dystrophy seem not to remain true to type and in certain cases characteristic signs of at least two of these types have been seen in one individual

LEWIS STEVENSON

MYOTONIA CONGENITA

(*Thomsen s Disease*)

This is a disease which usually affects several members of the same family and is transmitted from generation to generation The muscles are so affected that at the beginning of a muscular movement it is extremely difficult to overcome a certain muscular stiffness (hypertonus) After several contractions the muscle limbers up" but this disappears as soon as the muscle is at rest again The disease begins very early in life and is chronic It has been demonstrated at Bellevue Hospital and amply confirmed elsewhere that quinine hydrochloride 5 or 10 grains two or three times daily acts specifically in the removal of myotonic symptoms in this disease probably by chemical reaction on the neuromuscular junction

LEWIS STEVENSON

REFERENCE

Kennedy Foster and Wolf Alexander Arch Neurol & Psychiat 37 68 1937

MYATONIA CONGENITA

(*Oppenheim s Disease Amyotonia Congenita*)

This is a rare disease in infants which was described by Oppenheim in 1900 Clinically it is the very opposite condition to myotonia congenita The two terms are often confused During the first few months of its life the child seems paralyzed—the muscles are flabby and atonic and the deep reflexes are absent or very sluggish The legs are most severely affected but the trunk and arms are also involved The arms and legs hang loosely and the child cannot move them to any great extent The muscles do not atrophy or at least do not appear to The

demonstrated Botulism, and the paralytic form of rabies are said at times to produce the syndrome of Landry's paralysis Other micrococci resembling the pneumococcus have been known to cause the disease

Morbid Anatomy —The lesions in the *spinal cord* vary greatly in severity In certain rapidly fatal cases they are very slight while in others there is an extensive change resembling that of acute poliomyelitis There may be vascular lesions in the gray matter of the cord particularly in the anterior horns, or merely simple chromatolysis with displacement of the nuclei in the motor cells of the anterior horns

Symptoms — At the onset there is a feeling of malaise slight pain in the back and heaviness in the legs which become weak There may be fever at first and sometimes myoclonic twitching of the abdominal muscles Within a day or two the patient cannot walk because of weakness in the legs and the paralysis spreads rapidly upward, involving the trunk arm respiratory and throat musculature The bladder and rectal sphincters are not usually involved The mind remains clear Deep reflexes disappear in the legs and later in the arms As a rule there is no definite loss of sensation in the legs or elsewhere

Diagnosis —Although clinical diagnosis from the point of view of neurology is usually easy attempts should be made to determine if possible the causal agent Cultures from the blood and spinal fluid should be made by a pathologist who is familiar with poliomyelitis and epidemic encephalitis Animal inoculations are desirable

Probably the only feature which distinguishes Landry's paralysis from *ordinary acute poliomyelitis* and *acute infectious neuronitis* is its rapidly progressive course. The *acute myelitis* due to syphilis of the cord and to neoplastic invasion of the cord and meninges must also be differentiated In these conditions the definite sensory level which can usually be discovered rises as the disease progresses upward in the cord *Acute multiple neuritis* caused by alcohol or other toxic agents can be distinguished by taking a careful history and by the pain in the limbs and loss of sensation in the hands and feet The possibility of *periodic family paralysis* must be kept in mind and should be suggested by the history of previous transient paralysis

Prognosis —Death has been known to result within two days and to be delayed for as much as a month but it usually takes place within a week after onset. In rare instances when the lesion in the cord has stopped before reaching the medulla the paralysis has gradually disappeared within one or two years

Treatment —The treatment consists of administration of warm sponge baths or packs colonic irrigation repeated lumbar puncture and the exhibition of urotropin The patient should be disturbed as little as possible

LEWIS STEVENSON

DISEASES OF THE MENINGES

Diseases of the Dura Mater —*Malformations*—Malformations of the meninges are commonly associated with such bony defects as spina bifida constituting meningocele Spina bifida occulta may be accompanied by abnormal formation of the meninges Incorporation of the roots of the cauda equina or lower portions of the spinal cord causes degeneration chiefly of the posterior column Symptoms referable to this may not become manifested until adult life and may be confused with those of such other diseases as tabes

Disease of the dura mater itself probably produces no symptoms except some pain Only when it leads to pressure on the brain cord or nerve roots is there manifested more important evidence of the disease.

Malignant growths of a sarcomatous nature may originate in the dura mater most frequently at the base of the skull In the early stages this produces symptoms suggestive of some chronic inflammatory condition by its implication of the cranial nerves in advanced stages the symptoms are those of brain tumor Malignant growths may also extend into the dura mater from such structures as the vertebrae and produce no other symptoms than those of the bony disease until the nerve roots or the spinal cord are pressed upon The same may be said of tuberculosis and syphilis when they involve the dura mater

Morbid Anatomy —There is no constant lesion in the nervous system but the muscles become infiltrated by small round cells ("lymphorrhage" according to *Buzzard*) The thymus gland persists in some cases and lesions may also occur in the liver and thyroid gland Developmental anomalies such as duplication of the great toe, malformation of the aqueduct of Sylvius, etc have at times been associated with this disease

Symptoms —The chief complaint is usually rapid fatigability of certain muscles In attempting to comb the hair for example it becomes impossible to raise the arm above the head more than once or twice Some individuals also cannot chew without the rapid onset of fatigue in the jaws Speech becomes an effort, and may undergo some alteration (dysarthria), swallowing is difficult, and there may be a good deal of general weakness Ptosis develops in one or both upper eyelids and the face assumes a sad sleepy appearance as the result of combined ptosis and facial diplegia It is difficult for the patient to close the eyes tightly and diplopia is often caused by weakness of one or other of the extra ocular muscles Sudden attacks of dyspnea and collapse are frequent and often fatal but the disease may run a subacute or chronic course for many years and may even in some cases disappear temporarily or even permanently

The muscles affected neither undergo atrophy nor show the reaction of degeneration The characteristic electric reaction the myasthenic reaction, does however develop When the muscles are stimulated by faradic current repeated at intervals of seconds the muscular contractions become weaker with each stimulation and soon disappear After a short rest the muscle regains its normal excitability

Treatment —Adequate feeding is essential and in acute cases, absolute rest in bed Tonics are useful Electric therapy should be avoided Some cases have been benefited by the use of ephedrine sulfate A creatinine-free diet and glycine by mouth have recently been tried with promising results.

Walker introduced the treatment of myasthenia gravis by physostigmine in 1934 Since then the use of prostigmin has become quite general in the treatment of this disease Intramuscular injections of 3 to 5 cc of a 1 2000 solution combined with atropine once a day or at intervals of several days have proved useful Atropine is given to offset the effect of the prostigmin in producing intestinal cramps and other disagreeable effects Some prefer to give 1 cc of the prostigmin solution three times a day before meals and then atropine is not required Prostigmin is sometimes more effective by mouth when given in doses of 0 015 Gm two to six times a day in the form of prostigmin bromide In spite of this treatment these patients often die suddenly Kennedy and Wolf have shown that myasthenia and myotonia are primary disorders of muscle or the myoneural juncture, and the prostigmin facilitates the action of the vagus stuff in myasthenia and quinine inhibits this action in myotonia—at the myoneural junction

LEWIS STEVENSON

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LANDRY S PARALYSIS

Definition —Landry s paralysis is a form of acute ascending paralysis of the spinal cord, which was first described in 1859 and is still recognized as a clinical entity It is usually rapidly fatal

Incidence —The disease attacks for the most part healthy young adults, and frequently is preceded by influenza gonorrhea or other infectious diseases The author has seen it during epidemics of lethargic encephalitis, in one case except for the lack of sensory change it resembled the acute infectious neuronitis described by Kennedy

Etiology.—The causal agent is not always the same In some patients the condition is undoubtedly due to the virus of poliomyelitis while in others the virus of epidemic encephalitis or the acute infectious neuronitis probably plays the etiologic role although this has not yet been satisfactorily

1500 cells per cubic millimeter which produces turbidity visible to the naked eye is pathognomonic In acute meningitis most of these cells are polymorphonuclear leukocytes The formation of a pellicle in the cerebrospinal fluid after it has stood for several hours suggests tuberculous meningitis but may be associated with other types of leptomeningeal inflammation The spinal fluid may be so purulent that it only passes with difficulty through a needle of ordinary caliber The white cell count of the blood is usually high, as in other infections The temperature varies according to the virulence of the infection and its curve is usually of the septic type

PROGNOSIS—A benign form often designated *acute aseptic meningitis* may closely resemble tuberculous meningitis and in spite of showing as many as 2000 cells, usually lymphocytes per cubic millimeter usually recovers entirely after perhaps only one lumbar puncture and no further treatment

In other forms of meningitis the prognosis is serious, many patients dying within a few days Chemotherapy has greatly improved the prognosis of meningitis caused by meningococcus, yet has sometimes proved disappointing in the treatment of pneumococcal meningitis It should be pushed nevertheless as also in meningitis due to *Streptococcus haemolyticus*

Localized meningitis underlying fractures or forming an extension from a sinus or mastoid infection affords some measure of hope from combined surgical treatment and chemotherapy in appropriate cases

Residual defects such as mental defect paralyses and other manifestations of permanent damage to the nervous tissues are uncommon

TREATMENT—Lumbar puncture performed once or twice a day withdrawing 10 to 20 cc. of spinal fluid gives great relief The greater efficacy of continuous drainage is questionable but may be resorted to if the cell count does not fall with the first mentioned mode of treatment Hot packs and prolonged warm baths have a marked sedative effect Saline purges relieve intracranial pressure and eliminate toxins

Chemotherapy includes the use of sulfapyridine or sulfadiazine Either should be given early and an attempt made to sustain a level of at least 10 mg per cent in the blood The level in the spinal fluid should exceed half of this for satisfactory results Sulfathiazole does not penetrate the meninges satisfactorily An initial dose of 2 Gm followed by 1 Gm every two hours will usually effect the desired level which level can usually be maintained by 1 Gm every four hours for as long as there is evidence of bacterial activity If coma restlessness or vomiting should make oral administration difficult nasal tube administration of the drug as well as nourishment should be tried Failing this intravenous injection of the sodium salt in five per cent solution should be resorted to until one of the other methods become possible To conserve the veins the intravenous method can best take the form of a continuous drip to reach and hold appropriate levels Total fluids administered in twenty four hours should be kept between 1500 and 2000 cc unless dehydration is extreme at first

Unpleasant effects from these chemical agents are Gastro intestinal disturbances often controlled by bicarbonate of soda, cyanosis best treated by methylene blue in 2½ grain doses three times a day drug eruption not often requiring more than local applications fever that may be as high as 104° F but which will fall promptly on interruption of treatment if the spinal fluid count indicates that this may be done Hematuria especially if accompanied by a relative anuria may end in plugging the ureters with crystals necessitating immediate cessation of chemotherapy

Subarachnoid hemorrhages of apparently spontaneous origin are possibly much more common than has been suspected In a high percentage the serologic findings suggest syphilis as the etiologic agent but senility pregnancy endocarditis some of the severe anemias hemorrhagic diathesis and the acute infectious diseases may present this complication Some cases are ascribed to epidemic encephalitis Others result from congenital or preformed aneurysms

At onset the syndrome varies greatly Many patients have sudden severe headache with dizziness but no loss of consciousness These symptoms with marked stiffness of the neck may persist for weeks without other manifestations Prompt relief may fol

Infection (Pachymeningitis) —Metastatic abscesses of the vertebral bodies may irritate the outer surface of the dura mater and produce clinical manifestations suggestive of meningitis The spinal fluid, however, is free of cells and globulin though under increased pressure

In the skull extradural abscesses may occur from an extension of a mastoiditis or sinusitis usually frontal and ethmoid or may be the result of a head trauma This complication may give few symptoms beyond those of the original disease Thrombosis of the venous sinuses may be another consequence leading to chills, venous engorgement of the face and proptosis

Tuberculosis rarely affects the dura mater alone although tuberculous lesions (diffuse thickening or isolated tubercles) have been seen on both the brain and spinal cord

Syphilis not uncommonly causes chronic thickening of the dura mater usually over the cervical region of the spinal cord The diffuse pains in the neck shoulders and arms which are characteristic of this condition are very resistant to treatment Pressure on the motor roots may lead to muscular atrophy Claw hand is not an uncommon deformity Thickening over the cerebral hemispheres causes intractable headache localizing signs such as convulsions, or evidence of general paresis

Hemorrhage —Subdural hematoma is almost invariably the result of trauma At first it gives persistent headache often closely localized but later may exert sufficient inward pressure on appropriate centers to cause incomplete hemiplegia aphasia or hemianopia If this blood is not evacuated it becomes organized and *pachymeningitis interna hemorrhagica* with its characteristic chronic headache results Calcification of the clot is a less frequent late process

X rays of the head taken from before backward, may demonstrate this condition by the lateral shift of a calcified pineal gland

Diseases of the Leptomeninges —*Meningitis* —Inflammation of the leptomeninges may be caused by other organisms than the meningococcus tubercle bacillus and spirochete of syphilis As in the case of the dura mater the infection may be introduced by trauma extension from neighboring bony structures or by the blood or lymph Leptomeningitis may result from mastoiditis sinusitis, or trauma, if the dura mater has been penetrated This form of meningitis may occasionally remain more or less localized Significant evidence of such a condition is facial neuralgia, or paralysis of the face and eye muscles which results from involvement of the nerve supply by the exudate The type of meningitis derived from the blood stream frequently begins basally and produces about the same clinical manifestations but it more often involves both hemispheres

The lesion may vary in degree from a congestion and dulling of the luster of the pia arachnoid to a frankly purulent infiltration At times the purulent areas are more or less discrete especially in such crevices as the sylvian fissure or about the cerebellum

The constitutional diseases sometimes complicated by meningitis are endocarditis septicemias such as those of childbirth typhoid fever, and gonococcal infection or any of the infectious diseases, especially pneumonia The condition also results from such local infections as erysipelas of the scalp face and neck Although all types of organisms may produce the inflammation those most commonly recovered (direct smear or culture) are the pneumococcus and streptococcus

Symptoms and Signs.—The onset may be insidious particularly when the primary constitutional or local disease has been severe but it may also be fulminating when the condition develops as a complication of some other disease or as an apparently primary disturbance The early signs are headache malaise irritability, restlessness stupor or delirium Vomiting anorexia, and constipation are other common general symptoms Convulsions neuralgia and paralyses point clearly to the central nervous system as the site of the lesions Stiffness of the neck and Kernig s sign although characteristic may be absent and are not essential for diagnosis The reflexes are usually not affected but may be somewhat increased or abolished in the more severe cases. Lumbar puncture demonstrates that the spinal fluid is turbid except when the condition is particularly well localized A cell content of

and nerve fibers and usually more or less productive inflammation of granulomatous nature In acute traumatic myelitis an acute primary degeneration with some vascular reaction is characteristic.

In *chronic myelitis* the cord is usually shrunken soft, and pale Brownish pigment spots may be seen when there has been a preexisting acute stage with marked hemorrhagic reaction or hyperemia In luetic cases the pia is opaque When trauma has been the cause there are frequently fine adhesions between the meninges and marrow with calcified areas in the pia Microscopic examination reveals secondary degeneration with segmentation of the myelin and a progressive granular disintegration of the axis cylinders Proliferation of the ependyma and glia and small cavities caused by necrosis develop and there is cellular atrophy Distention of the perivascular spaces with granular debris is especially prominent when there has been preexisting inflammatory exudation Endarteritis is characteristic in syphilis

Symptoms.—*Acute Myelitis*—Infectious myelitis is usually rapid in onset and may be apoplectiform The constitutional symptoms which are usually present vary in severity Paresthesiae slight weakness limited to one or more extremities root pains, and disturbances of sphincter function are common prodromata When the condition is the result of syphilis however symptoms usually develop gradually In cases due to poisons and toxins either mode of onset may occur When trauma is causal symptoms appear immediately

The symptoms referable to the spinal cord depend less on the cause than on the level of the involvement and the intensity of the pathologic processes Even disseminated or extensive lesions often evoke a symptom complex referable only to one level of the spinal cord except when the cranial nerves are involved when the progress of the disease is gradual or when the cervical and lumbar enlargements are both seriously affected

Divisions of the Spinal Cord—For convenient description, the spinal cord may be divided into three levels a lesion in each of which produces a more or less distinct syndrome the cervical the dorsal and the lumbosacral which includes the cauda equina and conus Symptoms are referable to impaired function of the various cell groups and fiber tracts and may be classed as motor sensory reflex, visceral, and trophic in nature Some degree of paralysis and alteration of the tendon and superficial reflexes is prominent and present in all cases The other symptoms are more variable and may be present in mild degree only

1 CERVICAL CORD —When the cervical region of the spinal cord is affected, the symptoms can be classified as follows

Motor paralysis involves the upper and lower extremities to some degree flaccid in the upper and spastic in the lower If the damage is severe the involved extremities are flaccid at first High cervical myelitis usually ends in death within a few days Hyperkinetic phenomena are common and include fibrillary tremors in the arms and automatic movements in the legs

Sensory disturbances may be less severe than the motor They include hyperesthesia, paresthesia and root pain in the segmental areas involved with diminished sensibility below The type of sensory loss depends on the tracts involved.

Reflex—With the onset of acute and severe myelitis all reflexes are usually lost, although at times in the earliest stages all are exaggerated for a brief period The abdominal and anal reflexes may be retained for a day or two and the anal reflexes may be the only evidence that functional blocking of the spinal cord is incomplete Later the tendon reflexes return in the lower extremities the plantar responses become extensor in type and the confirmatory evidences of the Babinski phenomenon may be found In complete recovery the abdominal and cremasteric reflexes are usually the last to resume normal activity

Visceral—Among the visceral symptoms is retention of urine and feces with loss of bladder and rectal sensation Priapism is frequent It may be spontaneous or induced by catheterization or cleansing of the parts After a varying period usually about a fortnight the bladder becomes automatic and empties itself periodically Sphincter function as a rule returns early Permanent impotence may follow even mild myelitis.

Trophic—In severe cases prevention of decubitis is almost impossible Edema of the

low lumbar puncture and if this treatment is given every two or three days until the spinal fluid is clear the patient may be completely restored to health under favorable conditions Some patients particularly the senile suffer from great restlessness, delirium or mania during the hemorrhage and die from the resulting exhaustion At times unconsciousness, which develops slowly or suddenly according to the rapidity of bleeding is the first symptom Focal signs such as hemiplegia aphasia and visual disturbances are probably indications of clotting and organization over the appropriate areas or of actual laceration of the brain tissue by the hemorrhage

The spinal fluid may at first resemble pure arterial blood except that it does not tend to clot If centrifuged or allowed to settle the supernatant fluid has a yellowish or brownish tinge This discoloration may be considered evidence that the bleeding is not caused by a faulty lumbar puncture since such staining cannot develop until about twenty four hours after the manipulation

ROBERT G ARMOUR

MYELITIS

Definition —The term myelitis' should be restricted to pathologic processes and clinical conditions which are the result of trauma infection and toxins acting upon the spinal medulla alone Spinal apoplexy compression of the cord and degenerative involvement of the long tracts (as in tabes dorsalis and the various scleroses) are no longer classified as myelitis

Incidence —Myelitis as defined above is not common It is probable that variations in diagnostic nomenclature in various parts of the country make it impossible to state the actual frequency of myelitis as the term is used in this article. The term myelopathy is preferred in cases where tissue changes are not caused by direct infective inflammation

Etiology —The causes of myelitis are infection poisons and toxins and trauma If one excludes uncommon instances of epidemic poliomyelitis in which the fiber tracts and posterior horns are involved and the cases of virus infections limited to the spinal cord it can be said that there is no primary form of infective myelitis The list of infections in which secondary involvement of the spinal cord may occur is long A postvaccinal toxic or infectious myelitis may occur and is serious enough to compel caution in the use of immunizing sera and vaccines In cerebrospinal meningitis focal inflammatory damage to the spinal cord may occur In carbuncles and in chronic infections of the kidney bladder and pelvic organs lymphogenous extension to the spinal cord may occur Direct extension from empyema has been reported Embolism in septicemia and endocarditis may be responsible for myelitis *Toxic myelitis* may be due to poison by carbon monoxide carbon bisulfide or chloroform it may occur after spinal anesthesia and has been observed as a complication of subarachnoid injections of alcohol for the relief of pain In cachectic states and severe anemia the spinal cord may be affected Myelitis is not uncommon during pregnancy and the puerperium Whether the condition associated with the puerperium is toxic or due to a mild infection may be impossible to determine *Traumatic myelitis* may be the result of direct or indirect violence Electric shock and penetrating wounds produce local injury to the spinal cord but not myelitis of the type here considered

Morbid Anatomy —In the *acute stage* gross examination reveals a swollen somewhat soft and injected cord On cross section it may be difficult to distinguish the gray and white matter because of the hyperemia although in acute traumatic myelitis the cord may appear normal Microscopic examination reveals three abnormalities vascular inflammatory and degenerative which vary in proportion and degree with the etiology Edema and hemorrhages from the capillaries follow trauma and infection. Round cell infiltration in and outside the vessel walls and glial proliferation are noticeable only in infectious myelitis Toxic myelitis is characterized by edema and mild primary degenerative changes in the cells and myelin sheaths and by the absence of vascular reaction In luetic conditions vascular degeneration is prominent and endarteritis is often well developed There is also some edema with degenerative change in the cells

and nerve fibers and usually more or less productive inflammation of granulomatous nature. In acute traumatic myelitis an acute primary degeneration with some vascular reaction is characteristic.

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Trophic—In severe cases prevention of decubitus is almost impossible Edema of the

paralyzed extremities and abnormalities of sweat secretion may occur

2 DORSAL CORD —The dorsal region of the cord is most apt to be attacked by the sub acute or chronic forms of myelitis The symptoms of its involvement are the same as those of cervical myelitis except that the arms are not involved The patient may complain of paresthesiae in the upper ex tremities when otherwise there is no sensory loss higher than for example, the sixth dor sal segment This symptom may be impor tant in establishing the disseminated nature of the disease The upper abdominal reflexes are retained when the lesion is below the eighth dorsal segment

3 LUMBAR CORD AND CONUS —When the lumbar region and conus are attacked the paralysis which is confined to the legs, is flaccid in type and the paralyzed muscles atrophy The knee jerks are absent when the lesion affects the upper lumbar segments If the level of involvement is at the fifth lum bar and first and second sacral segments only the ankle jerks and the hamstring jerks are lost The plantar reflex is almost always abolished Incontinence results from paral ysis of bladder and rectum

Chronic Myelitis —When the onset of chronic myelitis is gradual the patient com plains chiefly of weakness This consists of heaviness and stiffness of the lower extrem ities when the dorsal cord is affected Pares thesiae may also develop in the legs and a girdle sensation or even lancinating pains corresponding to the segment involved Ob jective sensory impairment is deferred and less marked than the paralysis The patient may have his attention first called to the presence of a weakness by fatigability on exertion or long walking or he may observe that the thighs seem weak in going up or down stairs Should the segments involved be in the lumbar or cervical enlargements atrophic palsy of the muscles supplied by the affected segments develops gradually Disturbances of sphincter function are usu ally late in appearing

Traumatic Myelitis —Direct or indirect violence to the vertebral column may imme diately impair spinal cord function Injury without compression of the cord is often difficult to distinguish from the crushing lesions which result from displacement or fracture of the vertebrae The immediate result of even mild forms of trauma may be edema so profound that it completely abol ishes function at the level of injury, and constitutes what may be called a physiologic block The symptoms which result from simple concussion are practically the same as those due to contusion with diffuse petechial hemorrhages throughout the spinal marrow those referable to an injury at a given level are no different from the symp toms of the infectious and toxic type of myelitis except that root pains are frequent and prominent Degenerative reactions in the injured tissue will cause chronic residual symptoms

Disseminated myelitis may be a sequel to any infection and is often due to syphilis It is sometimes indistinguishable from acute multiple sclerosis The scattered lesions pro duce appropriate symptoms from the begin ning

Diagnosis —The anatomic diagnosis of well established myelitis is simple During the prodromal period of the acute form paresthesias or root pains weakness or dis turbance of sphincter function immediately arouse suspicion of myelitis *Acute rheu matic fever* in its early stages may simulat myelitis In the infectious form precedin; infectious disease is important Both foca and local infections must be searched for When a general infection is causal the myel itis is apt to occur in the lumbar and cervical enlargements because of their abundant vascular supply The spinal form of epidemic encephalitis and of epidemic poliomyelitis with involvement of the fiber tracts is dis cussed in other chapters

In toxic myelitis the onset is less abrupt Search for underlying constitutional or pre disposing environmental conditions is essen tial Differential diagnosis between toxic and mild infectious myelitis may be difficult Multiple neuritis may be difficult to dis tinguish Differentiation between acute mye litis and *spinal thrombosis or hemorrhage* is often practically impossible In elderly people with low blood pressure and in cachetic patients *thrombosis* should always be considered

Difficulties may arise in establishing the etiology of the subacute or chronic forms Syphilis is a common cause Naturally

chronic myelitis results from incompletely cured acute myelitis. *Kummels disease* may involve the vertebral column and in a small per cent of cases may compress the cord Adhesive arachnoiditis will often produce symptoms suggestive of chronic myelitis The laboratory aids to diagnosis are helpful A diagnosis of chronic myelitis implies the exclusion of *primary or metastatic tumors of the spinal cord and meninges vertebral disease combined sclerosis multiple sclerosis myelomalacia,* and *pachymeningitis with thrombosis or ischemia of the vessels of the cord* Erosion from aneurysms is rare but should be kept in mind

Examination of the spinal fluid is of special importance It is seldom that organisms can be cultured in the milder cases An *increase in protein and cell content is evidence* of inflammation. In *traumatic cases* the fluid may be discolored by pigment derived from blood and flow of spinal fluid may be blocked by swelling of the cord In subacute and chronic conditions when it is tinged with yellow, contains a marked excess of protein and few or no cells there is a compressing lesion which has disturbed its flow A partial or complete block of flow of spinal fluid during manometric examination by the Ayer method indicates some form of compression either neoplastic or inflammatory A positive Wassermann reaction which is the rule in *syphilitic myelitis* speaks for itself When there is an increase in protein abnormalities of the colloidal gold curve must be interpreted with caution especially when the Wassermann reaction is negative

Complications and Prognosis—*Unless the upper cervical region of the cord is involved* with ascent of the process to the medulla death seldom results from the myelitis itself Occasionally a case is seen in which the inflammation is so intense that abscess *formation* results with extension and widspread thrombosis Such a *condition* is always fatal The prognosis while always serious from the standpoint of complete restoration of function depends partly on the etiology and severity of symptoms and partly on the *complications The more complete* the loss of spinal cord function the less probable is complete recovery The type due to dissemination or extension of a local or focal infection as a rule causes death In syphilitic myelitis prompt and intensive specific treatment usually evokes a favorable response.

The serious nature of myelitis *often* lies in its *complications Extensive decubitus* is a forerunner of death, and in *paralysis of* the bladder an ascending infection of the kidney is always imminent

The rate of recovery varies considerably and one may be agreeably deceived Sensation *attains* its maximum improvement within three *to six months* and motor recovery is maximal within between six and twelve months Complete return of sphincter function is the rule in mild cases A spastic weakness of the lower extremities is the most prominent residual symptom When the primary stage of inflammation or softening *is chiefly exudative,* recovery is more rapid and complete than when *there has* been productive inflammation with degeneration or hemorrhage which produces scar tissue

In traumatic myelitis, prognosis may be *impossible* during the first two or three days *because complete physiologic* block produced by edema is clinically identical with crushing of the cord Examination of the spinal fluid at this time may not give definite data and deformity of the vertebral axis does not prove that the cord has been crushed Indirect violence may cause a momentary *dislocation of the lower cervical* vertebrae with varying degrees *of injury to* the spinal cord Improvement in traumatic myelitis may continue for an extended period of time Adhesions between the meninges and the cord, with at times local *accumulations of spinal fluid* may develop and be responsible for the delayed appearance of symptoms of compression Gliomatous changes in the spinal medulla have been known to develop they are associated with the syndrome of tumor of the spinal cord

Treatment—*The treatment of* myelitis includes first measures *appropriate* to the cause and second symptomatic *remedies* Counterirritation and diathermy applied over the most involved segments of the spinal cord given carefully are not objectionable There *is no satisfactory* local treatment and general nursing *really comprises* the entire therapy in acute or severe cases

without a cause which can be specifically treated Because of the susceptibility to decubitis, especially with lesions of the lumbosacral enlargement, it is wise to place the patient on an air bed The body must be kept clean and dry Frequent changes of position are helpful Application of protective pads to the heels and sacrum is quite necessary In the diet plenty of 'roughage' is desirable to prevent constipation Colon irrigation every three days and daily oil enemas serve to keep the alimentary tract clean Management of the bladder is perhaps the most important single item When there is incontinence, some urine is usually retained In patients with retention it is wise to avoid catheterization for it is very difficult to avoid infecting the bladder directly by routine catheterization Rupture of the bladder and hydronephrosis are equally rare Cystitis is a serious and intractable complication which is particularly liable to be associated with lesions of the lumbar enlargement or conus when the trophic nerve supply is impaired A retention catheter may be necessary Manual expression at regular intervals when performed skillfully usually serves to relieve intense distress until either there is improvement or the bladder becomes automatic A belladonna suppository or a hot enema may help start the flow of urine when there is retention

A tent at the foot of the bed to keep the covers off the feet is useful Slight elevation of the lower extremities aids return circulation and decreases edema Very light massage and limited passive motion should be given to the paralyzed extremities after the first fortnight to aid in maintaining circulation and preventing contracture No stimulating measures or electricity should be employed during the acute stages Should a bed sore develop dry dressings must be applied at first If there is wide extension and necrosis, a wet dressing is preferable

When the extremities are spastic light massage and mild galvanism or diathermy may be given Reeducative exercises are desirable for patients with persistent spasticity or ataxia For severe contracture surgical measures including tenotomy neurectomy, and muscle transplantation are to be considered Orthopedic appliances may enable the patient to walk Electrotherapy finds its chief use in cases with persistent flaccid palsy

In traumatic myelitis it is important to be certain that there is no deformity of the vertebral axis Laminectomy should be performed without delay when the cord is compressed This is almost always due to displaced vertebrae or fragments of bone, it is very rarely due to meningeal hemorrhage It may, at times be due to edema sufficient to cause not only physiologic block but mechanical compression of the cord This is indicated by obstruction to the flow of spinal fluid

GEORGE H HYSLOP

SUBACUTE COMBINED SCLEROSIS OF THE SPINAL CORD

Subacute combined sclerosis of the spinal cord is a progressive condition of middle life the course of which is variable and dependent upon associated conditions and their treatment It is characterized by sensations of numbness and tingling of the hands and feet and by increasing paralysis of the legs and hands It results from degeneration in the posterior and lateral columns of the spinal cord Anemia and *achylia gastrica* accompany the morbid process in the central nervous system

Although twenty years ago this disease was thought rare it is now comparatively common This increase in incidence may be due in part to improved methods of diagnosis

Etiology —At one time the disease was believed to be the result of pernicious anemia but it is now known that the symptoms produced by changes in the spinal cord often precede those of deterioration of the blood *Free hydrochloric acid* is usually absent from the gastric contents in the early stages of the disease This lack was once thought to be instrumental in promoting absorption of the toxic material from the gastro intestinal tract and thus cause deterioration of the spinal cord and the elements of the blood At the present time the lesions are believed to be due to deficiencies of some vital factor and perhaps of vitamins

The disease may first appear in the train of other exhausting disturbances such as

cancer or any prolonged illness but just as often it develops without apparent cause

Incidence—Combined spinal sclerosis is rare in individuals less than thirty five years of age or more than sixty five The incidence is highest in patients between forty five and fifty five The sexes are equally affected

Morbid Anatomy—Usually there are no lesions above the medulla and the spinal cord remains macroscopically unchanged Microscopically extensive degeneration is evident—chiefly in the middorsal region affecting the posterior tracts the direct cerebellar tracts, and the direct and indirect pyramidal tracts For the most part this is restricted to a discrete system The peripheral nerves also may be involved

Symptoms—The patient may have had vague dyspepsia for some years before he gradually becomes aware of a sensation of deadness and pins and needles' in the tips of the fingers of both hands and in the toes of both feet These sensations are symmetric and practically synchronized in all four limbs At first they are sharply limited to the extremities of the limbs only in the advanced stages of the disease do they extend to the elbows or the knees

No further symptoms may occur for some months even without treatment Then however unsteadiness of gait ataxia especially in the dark and poor stereognosis with consequent manual clumsiness may appear Examination at this stage shows the cranial nerves to be normal There may be sensory ataxia in the arms as in tabes Astereognosis dependent on impairment of the sense of position in the fingers is often accompanied by a lowering of vibration sense as well The abdominal reflexes are depressed or absent The knee jerks usually remain active Absence of ankle jerks and a bilateral Babinski phenomenon are signs of degeneration of the posterior column and the motor column respectively Sensory losses in the lower as in the upper limbs produce ataxia and a positive *Romberg sign* The sphincters at this stage are rarely affected

The intellectual faculties may deteriorate and occasionally in advanced stages a mild delirium appears

In most instances the disease is progressive Girdle pains are felt as tightness and pressure rather than as shooting pains, as in tabes Acute abdominal distention in attacks of several days duration bladder and rectal retention and incontinence and increasing weakness and ataxia of the legs and arms within a year render the patient bedridden The knee jerks will then probably have disappeared and increased losses of posterior column sensations will be found in the legs and hands but a double extensor response can usually be elicited until death Progressive prostration accompanies these local disabilities and if as is usual there be continuous blood decline the deterioration of general function is thereby accelerated Mental disturbance bed sores and total palsy of limbs and sphincters constitute the symptoms of the last stages Death is usually the result of heart failure or intercurrent pulmonary infection It may also be caused directly by neural dysfunction as evidenced by bedsores or cystitis due to retention of urine

Diagnosis—The outline on page 1392 may be useful in solving the difficulties which often arise in distinguishing subacute combined sclerosis of the cord from multiple (disseminated) sclerosis multiple neuritis and tabes dorsalis

In any of these symptom-complexes the presence of achylia gastrica or deterioration of the blood or both enormously increases the probability that the concomitant nervous symptoms are manifestations of subacute combined sclerosis of the cord

Treatment—Search should be made for areas of infection or toxemia The teeth should be examined and also the tonsils and sinuses The malign influence of a sepsis of the gallbladder in initiating the process which ends in pernicious anemia or subacute combined sclerosis of the spinal cord has already been mentioned

Some reliable preparation of liver extract forms the basis of treatment in this disease The introduction of this therapy has greatly improved the prognosis of cases of combined sclerosis of the cord It must be emphasized that the cord symptoms do not occur *pari passu* with or as a result of the anemia but the cord symptoms are influenced for the better by liver therapy and in some cases the cord changes themselves are checked by this agent Parenteral liver extract given in

Subacute combined sclerosis of the cord	*Multiple sclerosis*
Incidence highest between forty five and sixty	Incidence highest between twenty and thirty five years of age
Progressive course	Remittent episodic course.
No ocular symptoms	Transient blindness or blurring of vision
	Transient double vision
No change in the optic nerve	Pallor of the temporal portion of the optic disks
Sphincter trouble in late stages	Sphincter trouble in early stages
Deep reflexes usually absent.	Deep reflexes rarely absent

Subacute combined sclerosis of the cord	*Multiple neuritis*
Associated with Addison s anemia	Cause may be avitaminosis bacterial toxins and various other poisons
Usually no muscular tenderness	Muscular tenderness
Loss of posterior column sensation loss of the senses of position vibration and deep pain	Loss of peripheral sensation loss of superficial sensation of glove and stocking type
Abdominal reflexes absent Double extensor plantar reflexes	Abdominal reflexes present, and extensor plantar reflexes absent
Sphincter palsy in late stages	No sphincter involvement
Motor palsies referable to cord	Peripheral motor palsies (dropped wrists and feet)

Subacute combined sclerosis of the cord	*Tabes*
No history of syphilis Tests for syphilis negative	Positive history of syphilis Syphilitic tests positive, usually
Cerebrospinal fluid normal	Lymphocytosis in spinal fluid Wassermann test positive usually
Pupils normal	Pupils fixed or sluggish in response to light
Great loss of motor power	Slight loss of motor power
Extensor plantar reflexes	Flexor plantar reflexes
Rare lightning pains	Common lightning pains

tramuscularly once or twice a week is much more effective than mouth feeding the sphincter symptoms appear to be particularly amenable to this mode of therapy Vitamin B complex is especially effective in the peripheral neuritis which frequently accompanies the condition Arsenotherapy is contraindicated

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MULTIPLE SCLEROSIS

(*Insular Sclerosis Sclerose en Plaques Disseminated Sclerosis*)

Definition—Multiple sclerosis is a diffuse disseminated structural disease essentially to the central nervous system characterized by a degeneration in multiple areas which leads to widely diversified symptoms often of transient character involving chiefly the motor system

History—The first recognition of the disease is credited to Cruveilhier (1835) although it was Valentiner (1856) who first tentatively described the symptomatology Charcot and Bouchard (1862–1863) clarified the conception of the syndrome and established the triad of signs—nystagmus scanning speech, and intention tremor—as pathognomonic of the disease Since the important monograph by Bourneville and Guérard appeared in 1869 the literature on the subject has become voluminous through investigations in Germany Scotland and later in the United States

Incidence—The disease occurs most frequently in young adults its onset is rare in patients less than fifteen and more than thirty five years of age Evidence thus far obtained points to its greater prevalence in Europe than in America Multiple sclerosis is one of the commonest organic diseases of the nervous system and by some observers has been regarded as even more prevalent than syphilis Further statistics should be obtained

Etiology—The cause of the disease is entirely unknown Infections thermal influences traumatism and intoxications by lead arsenic and the like have been regarded as possible etiologic factors The disease has been attributed to various micro organisms but no substantial evidence has been presented in support of any of them

Morbid Anatomy—The macroscopic changes are widely distributed throughout the central nervous system irrespective of gray or white matter and the special neuron tracts They appear as areas of degeneration

of varying size often sharply circumscribed mainly perivascular In the acute stage the lesion is edematous, but once the fluid has been absorbed contraction and sclerosis occur These stages correspond to the acute onset of symptomatic episodes and their remission Microscopic examination invariably reveals a primary change (tumefaction) of the myelin sheaths, followed much later by a certain degree of axon destruction This early myelin degeneration constitutes the sclerotic patch characteristic of the disease Changes in the neuroglia are secondary The reason for the disparity often observed between the apparently destructive pathologic lesions and the symptoms is the persistent preservation of the conducting axons in spite of extreme myelin degeneration The characteristic tendency to remissions is explained also by the restoration of axon function in affected areas through which in the acute stage no conduction was possible The roots of the spinal nerves may undergo change similar to that in the brain and cord

Symptoms —As would be expected from the pathologic changes the syndrome of multiple sclerosis is more varied than that of any other single organic disease of the nervous system The three classic symptoms nystagmus scanning speech and intention tremor, appear very inconstantly and are by no means essential to diagnosis Because of the multiplicity of the lesions and the varying sequence of their appearance in different parts of the cerebrospinal axis the resulting signs and symptoms must be irregular in character and development Spastic conditions in general predominate muscular atrophy is rare sensory disturbances are definitely subordinate to motor defects and pain seldom occurs A recent tabulation gives the following signs in order of diagnostic importance fatigue increase of deep reflexes nystagmus ataxic tremor of upper extremities and head loss of abdominal reflexes disordered gait and station disturbances of speech (often scanning) pallor of the optic disks on the temporal sides uncontrolled emotionalism remissions transitory palsies of ocular nerves vague sensory disorders vesical difficulty and mental changes Much stress should be placed on the frequent development of spastic conditions at some stage of the disease and less upon the supposedly characteristic tremor and scanning speech Spastic conditions are more likely to occur on account of the length of the motor (pyramidal) tracts than are nystagmus scanning speech, or motor ataxia, which have a much more limited cerebellar localization A tendency to remissions is a second most important symptomatic peculiarity

Diagnosis of so called typical cases' presents no difficulties In no other condition do the speech defect the ataxia on intended movement and nystagmus coexist in the same degree but this very fact has led to much confusion Experience has shown that the so called *Charcot triad* is so inconstant that it should not serve as a diagnostic criterion When present its evidence is conclusive, when absent as in a large proportion of cases other groupings of signs and symptoms should be considered *i e* spasticity loss of abdominal reflexes transient palsies in various nerve distributions tremors and atypical speech defects emotional instability and an irregular course That such a disorder with its recognized pathologic basis may simulate various functional and organic diseases is evident If this fact be borne in mind mistakes in diagnosis should be less frequent Examination of the spinal fluid affords some help in that a paretic gold sol curve is very frequently demonstrable (50 per cent of Ayer s series) as well as certain minor changes in the cellular content and other constituents A consistently negative Wassermann reaction in blood and spinal fluid distinguishes the disease from the various forms of syphilis with which in its purely clinical aspects it is often confused

Prognosis —Multiple sclerosis is always a long standing disease total recovery from which is doubtful The strong tendency to remissions may simulate recovery but evidence that recovery has actually taken place in any unquestioned case is still lacking It is not commonly in itself fatal The writer has seen many undoubted examples of this disease who in the course of twenty years have been able to maintain active living

Treatment —Since the cause of the disease is as yet undetermined there is no specific or really efficient treatment The possi

bility that a spirochete may be the cause is still too vague a basis for systematic treatment Silver arsphenamine sodium cacodylate and mercury have been given with some evidence of benefit Recently, patients have been treated with malaria and with typhoid vaccine in addition to malaria, but without beneficial results although some were temporarily improved Vitamin B intravenously or intramuscularly in doses of 100 or 200 mg daily or on alternate days is often definitely helpful In general symptomatic therapy and mechanical measures must be employed to combat the various manifestations as they arise

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DIFFUSE AND FOCAL DISEASES OF THE SPINAL CORD

Affections of the Blood Vessels of the Spinal Cord—Branches of the anterior spinal artery enter the central part of the cord through the ventral fissure and supply all the gray matter except a large part of the posterior horn Branches from the posterior spinals penetrate from the periphery into the white matter of the posterior column. Although the white and the gray matter are not supplied by two independent systems there are regions of the cord in which the gray matter receives its supply exclusively from the central arteries, and the peripheral white matter obtains nourishment only from the vasocorona The veins of the spinal cord are arranged like the arteries except that they are much more in evidence on the surface of the cord

Anemia—The rapid development of paralysis after profound hemorrhage may perhaps be explained by resulting anemia of the spinal cord Intermittent claudication of the spinal vessels with temporary level phenomena has also been described

Endarteritis and Arteriosclerosis—Endarteritis of the cord is part of a general process associated with lues or senile atheroma Foster Kennedy and Elsberg have observed sclerotic changes in the vessels of the cord in individuals with neuritis of the cauda equina

Arteriosclerosis of the cord is of several types that characterized by senile degeneration of the posterior columns and clinical evidence of posterior sclerosis (diminution of the deep reflexes and disturbances in postural and vibratory sense), that which involves the lateral columns and gives rise to spastic paraplegia without sensory changes or cystic symptoms and that evidenced by softening of the cord (myelomalacia) with scattered lesions in both the white and gray matter, and with symptoms of disease of the anterior horn cells (isolated atrophy with electric change in the muscles involved) In the author s experience the first type has never been associated with the clinical manifestations of posterolateral sclerosis (anemia achlorhydria) The symptoms in posterolateral sclerosis are probably due to the introduction of a myelolytic enzyme by way of the blood vessels while similar symptoms in arteriosclerosis of the spinal vessels are to be explained on the basis of advancing ischemia.

Spinal thrombosis may give rise to the Brown Sequard syndrome and syringomyelic disturbances are known to occur in pachymeningitis luetica after blocking of the lumen of the spinal vessels by organized exudate

Meningeal hemorrhage may be epidural intradural or subdural the epidural type is usually the result of trauma which ruptures the venous plexuses intradural bleeding less

frequently follows injury Both epidural and intradural hemorrhages are relatively unimportant because they are merely coincidental phenomena of a more severe lesion Subdural hemorrhage may follow trauma to the nervous system and is also frequently associated with obstetric injury convulsions fever, and hemorrhagic diathesis It is much more common than the extradural type It rarely leads to compression of the cord The most frequent cause of subarachnoid bleeding is rupture of an aneurysm at the base of the brain In some cases of apoplexy however the blood may find its way into the ventricles of the brain or into the subarachnoid space, and appear in the spinal sac These are cases which usually end fatally

Symptoms —In some instances meningeal hemorrhage produces no symptoms but as a rule its onset is marked by sharp pain in the back and symptoms referable to the nerve roots. There may be muscular spasms or paralysis of the arms or legs Except in instances of rupture of an aneurysm at the base of the brain there are no cerebral signs The cord symptoms depend on the level of the lesion

Prognosis —The prognosis varies with cause Recovery may ensue in cases of hemorrhage associated with constitutional disease.

Treatment —Since the cord is rarely compressed the operative removal of blood clots from the spinal cord seldom gives relief

Hematomyelia (Apoplexy of the Cord) —In comparison with apoplexy of the brain that of the cord is infrequent It occurs most often in individuals between twenty and forty years of age and is more frequently observed in men than in women It may be a complication of syringomyelia

Etiology.—Bleeding into the spinal cord is apparently not due to the same cause that evokes cerebral bleeding although the sclerotic changes associated with the latter syndrome are not uncommon in the spinal arteries The most important etiologic factor in spinal cases is *trauma* The spinal column itself may not appear to be injured and yet hemorrhage may ensue A fall on the buttocks or the legs direct injury to the spine sudden forward flexion of the head or a headlong dive may give rise to hematomyelia The lifting of a heavy load and military drill are also known to be precipitating factors Inflammatory and neoplastic lesions may serve as predisposing factors Spinal hemorrhage is favored by an underlying diathesis Arteriosclerosis seldom causes bleeding into the cord or its membranes Difficult labor may be a cause of hemorrhage in the newborn

Morbid Anatomy —Although hemorrhage may occur at any level it is most often found in the cervical enlargement The bleeding may extend throughout the gray matter or be restricted to one side of the cord and spread only in a vertical direction Frequently even when there are no apparent abnormalities on the surface of the cord palpation with the finger may reveal swelling The color of the cord may be bluish red because the blood clot shines through the surrounding white matter The extravasation is in some cases limited to one or two segments in others it extends through many levels and frequently it assumes a spindle like shape Since the gray matter contains more blood vessels and is a looser tissue than the white matter the latter is seldom involved except at the site of maximum hemorrhage. The lateral columns are usually spared When the lesion is of very long standing the pathways of the hemorrhage are represented by a cyst containing clear fluid

Microscopic examination of the cord lesions in the fresh cases reveals edema and necrosis After a few days evidence of glial proliferation can be found and granular cells abound later only local sclerosis remains If the anterior horn cells are destroyed atrophy of the ventral fibers is apt to ensue

Symptoms.—The symptoms usually begin suddenly and suggest a transverse lesion of the cord The patient falls to the ground as the result of weakness in the legs and exhibits sensory changes and disturbances in control of the sphincters Trophic phenomena soon appear At times the symptoms are less fulminating and the complete syndrome does not develop until secondary necrosis and inflammation have taken place At the onset there may be pain in the back and stiffness In mild cases symptoms are either lacking or so slight as to suggest a functional disorder When this occurs only very

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Meningeal hemorrhage may be epidural intradural or subdural the epidural type is usually the result of trauma which ruptures the venous plexuses intradural bleeding less

the meninges and nerve root sheaths A common form is the dural endothelioma or psammoma *Primary vertebral tumors* are sarcoma, osteoma and chondroma, of *metastatic tumors*, vertebral carcinoma is frequent. Less frequently other metastatic forms syphiloma tuberculoma and cysts involve the cord and related structures

Symptoms.—The following course typifies an extramedullary intradural tumor in the middorsal region Superficial pain of varying intensity and duration is due to a gradual compression of sensory roots at a definite segmental level This pain is frequently described as a feeling of constriction or as a girdle sensation and visceral disease may be suspected Coughing or straining may aggravate pain by increasing spinal fluid pressure Symptoms of cord compression then appear producing spastic paraplegia with subjective stiffness in the legs increase of the lower tendon reflexes and pyramidal tract involvement such as extension of the great toe on plantar stimulation (Babinski sign) Objective sensory disturbances are manifested by diminished perception of superficial sensation below a definite segmental level at which there may be a zone of hyperesthesia. Complete interruption of cord conduction by compression results in spastic paralysis clonus, superficial and deep anesthesia below the level of the lesion loss of anal and rectal sphincter control and automatic cord reflexes such as involuntary movements of the legs and automatic bladder

Diagnosis—Compression of the spinal cord eventually blocks the subarachnoid space and the circulation of cerebrospinal fluid and changes occur in the fluid below the compression which are of considerable diagnostic importance Froin described a rapidly clotting fluid of canary yellow color rich in protein to which he gave the name *xanthochromia* In cases of early compression Nonne found an increase in protein content without change in color clotting time or cell content Ayer has advocated combined cisterna magna and lumbar puncture in order to study respective pressures and flow of fluid in cases of suspected block Jugular compression normally increases spinal fluid pressure and flow In block such is not the case below the lesion and may be demonstrated by spinal puncture (Queckenstedt test)

Injection of air or of lipiodol (iodized poppy oil) into the subarachnoid space may show deformities or blocking of this space demonstrated by the roentgen ray thus indicating tumor

The upper level of cutaneous sensory loss is of great importance in determining the spinal segment involved Certain anatomic relationships however must be kept in mind In the upper cord the tumor is often sought for *too low* because the anesthesia is lower than the involved segment This has been ascribed variously to sensory skin overlap delayed crossing of sensory fibers within the cord or compression of the superficially placed laminated fibers of the lateral spinothalamic tract supplying lower sensation Unilateral disturbance of vibratory sensation indicates that the tumor is located on the same side Less often the tumor is sought for *too high* due to edema of the cord above the lesion or to compression of sensory roots which have a long intraspinous course as in the lumbosacral region It must be remembered that the vertebral bodies and spines and the cord segments have a different numeric relationship and suitable charts or tables must be consulted to ascertain the spinal level after the involved cord segment has been determined

Sensory conservation or relatively less involvement of the lower sacral dermatomes is *frequently found in cases of extramedullary* tumors Thus a conserved area of riding breeches design is explained by the anteromesial location of the tumor which involves the inner lateral spinothalamic laminations but spares those more peripherally placed For a similar reason the sensory skin disturbances for pain in intramedullary tumors more nearly correspond to the segmental location of the cord lesion Tumors anterior to the dentate ligament sparing the posterior roots may be painless Spinal tenderness on percussion opposite the affected segment is frequently present and is an important localizing sign Atrophies are important in localization and the same root and segmental relationships must be considered as in sensory signs Intercostal atrophy is of particular value because of the unisegmental innervation of intercostal muscles The

careful search reveals the isolated muscular atrophy (with electric changes), the slight but characteristic sensory disturbances and the fibrillation

Many of the symptoms depend on the location of the hemorrhage If it occurs in the lumbar region there is flaccid paralysis of the lower extremities with loss of the deep reflexes sensory changes involving pain and temperature for the most part (dissociated type) and atrophy of the muscles When the cervical enlargement is the site of the lesion, as it often is atrophic paralysis of the upper extremities and spastic paralysis of the lower limbs (spinal hemiplegia) result Involvement of the lower cervical cord may give rise to sympathetic phenomena (miosis pseudoptosis and enophthalmos) Taylor and Collier describe papilledema in cases of hemorrhage of the upper cervical cord and the author has also observed choked disks with this lesion. The hemorrhage may extend upward to the medulla and even into the pons Very frequently an acute Brown Séquard syndrome develops, with partial atrophic paralysis of the arm, spastic paralysis of the corresponding leg and contralateral disturbances in the pain and temperature senses At times the symptom complex is that of a transverse myelitis The writer has observed bladder and rectal symptoms and a typical 'riding pants' anesthesia in instances with bleeding into the conus Patients who survive improve markedly within a few weeks The paraplegia diminishes the bladder may recover its function and only those symptoms which are due to permanent damage to the cord (degenerative atrophies and the dissociated sensory disturbances) remain

Diagnosis —Hematomyelia must be differentiated from *meningeal hemorrhage* which is characterized by pronounced root phenomena pain in the back, and stiffness and tenderness of the muscles In epidural extravasation, however there is little pain Lumbar puncture helps to differentiate epidural from subarachnoid bleeding Hemorrhage into the spinal cord must also be distinguished from *acute myelitis* This is usually less sudden in onset is associated with fever, and runs a more protracted course *Thrombotic softening* of the cord caused by obliterating vascular disease may be recognized by the usual luetic history positive serologic data (blood), and by the evidences of definite spinal level involvement *Acute poliomyelitis* is, of course not associated with objective sensory disturbances

Prognosis —Except in those instances in which there is a severe transverse lesion or extension of the process to the medulla, the condition usually improves Complete recovery, however is rare Invasion of the phrenic area renders prognosis poor

Treatment —In the treatment of hematomyelia *absolute rest for two or three weeks* is essential The patient should assume the lateral prone posture and avoid coughing and straining at stool Care must be taken to prevent decubitus and bladder infection Later, warm baths and electric therapy are desirable Epidural hemorrhage may be treated surgically

E D Friedman

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TUMORS OF THE SPINAL CORD AND RELATED STRUCTURES

Primary tumors affecting the cord may arise from the cord substance proper from the spinal canal or from the vertebrae They are accordingly classed as intramedullary extramedullary or vertebral growths Extramedullary tumors may be further classified as intradural and extradural. *Hour glass tumors* partly intra and partly extravertebral, are named from the constricted mid portion which traverses the intervertebral foramen The most common primary intramedullary tumors are the ependymoma glioma and hemangioblastoma, the most frequent primary extramedullary tumor and indeed the most frequent of all cord tumors is the fibroblastoma arising from

magnum Tumors high in the cervical region which implicate the foramen magnum may simulate brain tumor in that they cause papilledema bulbar symptoms and occipital headache due to cervical root pressure

Treatment —Practical recovery has followed the surgical removal of extramedullary tumors with symptoms of marked compression In intramedullary tumors cysts may be evacuated and pressure symptoms relieved Posterior root section or chordotomy may be performed for intractable pain such as often occurs in vertebral carcinoma Deep x ray therapy may be used in inoperable cases, in cases of incomplete removal or in patients who refuse operation

Walter F Schaller

SYRINGOMYELIA

True syringomyelia or cavity formation within the cord is due to degeneration of poorly nourished glial tissue formed from primitive ependymal cell rests The cavitation occurs most frequently in the cervicodorsal region and usually begins in the posterior horns or about the central canal Cavitation may accompany *dysraphia* or occur secondarily and as a complication from cord hemorrhage chronic adhesive meningitis or degeneration of an intramedullary cord tumor Sensory dissociation is characteristic as the pain and temperature fibers which cross in the anterior commissure are involved in the lesion whereas touch fibers ascending in the posterior columns are spared Painless burns and injuries are symptoms which should lead the clinician to suspect this disease Central pain is an occasional symptom The anterior horn cells and lateral pyramidal tracts may be involved directly or by pressure causing muscular atrophies and spasticity of the extremities The vertebral column may be scoliosed from atrophy of spinal muscles and the thorax deformed (*thorax en bateau*) Trophic changes are frequent Unusual forms of syringomyelia are *analgesic panaris* (Morvan s disease) and *syringobulbia* *Peripheral neuritis leprosy* and *intramedullary cord tumor* are to be considered in differential diagnosis The course is chronic and progressive

Treatment should attempt to arrest the disease Deep x ray therapy is indicated Surgical drainage of the cavities by relieving pressure has given symptomatic relief

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DIFFUSE AND FOCAL DISEASES OF THE BRAIN

APHASIA

Definition — Aphasia, as ordinarily understood is a disorder of language of either the emissive or receptive type which is produced by a lesion in certain regions of the cerebral cortex or subcortic nerve fibers usually on the left side of the brain

History —Gall about 1800 was the first to suggest that the brain was made up of organs which controlled the "vital and moral faculties of man" Gall was not a quack and not the phrenologist he is usually described to be, but a scientific pioneer in brain physiology and his work had a great influence on the thought of his time He believed that speech and the memory for words were situated in the frontal lobes

About 1861 Broca began to give us our first important knowledge of speech defects due to lesions of the left hemisphere His ideas were based on certain cases of aphasia in which the brain was examined after death Lesions were found in the posterior part of the second and third frontal convolutions as well as elsewhere in the brain Broca described some of these speech defects as "aphemie" although he divided cases into two groups—"aphemie" and "amnesie verbale." The aphemic patient is able to understand what is said to him and can recognize words although he cannot pronounce or repeat them His vocabulary is reduced so that he can say nothing at all, or perhaps only a few short words or oaths The amnesic patient can speak and pronounce words correctly but they may have no meaning at all Broca believed that aphemia" was produced by a lesion in the third frontal convolution of the left side

The left inferior frontal gyrus of the brain is known as Broca s convolution" Broca s area lies within Broca s convolution embracing the base of the inferior frontal gyrus It extends, perhaps also to the adjacent part of the lowest region of the precentral convolution and to the anterior part of the insula.

Trousseau supported Broca s views in the discussion which followed Broca s papers and introduced the word "aphasia to replace Broca s "aphemia."

Brown Sequard syndrome, at least incomplete, is produced by extramedullary as well as intramedullary tumors In certain cases there are no absolute diagnostic criteria by which intramedullary and extramedullary tumors may be differentiated Tumors in certain parts of the spinal axis have distinguishing features cervical tumors may produce quadriplegia and involve the ciliospinal center and phrenic nerve Vertebral carcinoma may simulate an hysteric state because of loss of emotional control produced by pain Tumors of the conus evoke a characteristic riding breeches anesthesia early loss of sphincter control and symmetric peroneal palsy and foot drop loss of ankle and retention of knee jerk by involvement of the sacral centers Caudal tumors are characterized by severe bilateral sciatica like pain and palsy of the lower motor neuron type This may be relieved by sitting or lying with the lower limb flexed to relieve root tension

Cord tumor may be suspected in any case of painful paraplegia of gradual onset *Sub acute combined sclerosis* may be difficult to differentiate in the early stages if the usual anemia is absent Paresthesia absence of definite pain achlorhydria and marked disturbance of deep sensation with preservation of superficial sensation are important differential guides *Erb s syphilitic spastic paraplegia* usually has syphilitic signs and positive serology *Myelomalacia* (*transverse myelitis*) and *meningomyelitis* are of acute or subacute onset Syphilitic *meningomyelitis* may be confusing although the biologic aspects of the fluid are often deciding factors *Multiple sclerosis* although characterized by spastic paraplegia usually has other cardinal symptoms *Amyotrophic lateral sclerosis* and *primary lateral sclerosis* are pure motor syndromes *Syringomyelia* may closely resemble intramedullary cord tumor and indeed has been considered by some writers as due to necrosis in a glioma *Tuberculosis* of the spine is frequently evidenced by spinal deformity or the roentgen ray *Hypertrophic cervical pachymeningitis* may simulate an extramedullary growth and forms in effect a tubular growth with marked root pain and atrophy in the cervical distribution *Herniation of an intervertebral disk* may simulate tumor by compression *Adhesive arachnoiditis* may cause cystlike formations which compress the cord An *inflammatory disease of the cauda* described by Kennedy and Elsberg may be impossible to distinguish from tumor Developmental abnormalities such as basilar impression (platybasia) and the *Arnold Chiari* deformity may compress the cord at the foramen

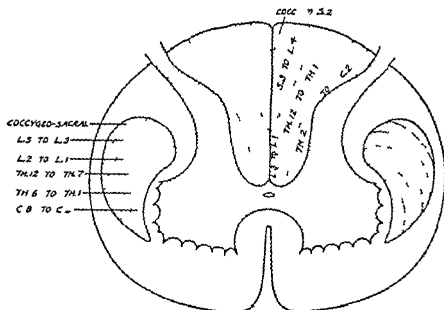


Fig 190 —Diagram to show lamellar arrangement of fibers in posterior column and in spino-thalamic tract (Purves Stewart, The Diagnosis of Nervous Diseases)

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Hughlings Jackson in 1864 began to write about the subject in quite a new way attempting to tell us more particularly the nature of aphasia He pointed out that aphasia on the emissive side is the inability to form or express a proposition in words and on the receptive side it is a failure of the mental processes which under lie perceptual recognition of a proposition—the more abstract the proposition the harder it is for an aphasic to formulate it or on the other hand, to understand it The work of Jackson was of great importance in many other ways and is only now receiving its full measure of appreciation

Bastian (1869) and Baginsky (1871) began to introduce schemas and diagrams of the speech centers and their relations to one another by nerve pathways attempting to reduce the knowledge of the subject to mathematic exactness and to postulate many theoretic types of aphasia Bastian described word deafness

Wernicke in 1874 localized the center for auditory images in the first left temporal convolution He believed that oral speech alone possessed cortical centers one guiding and the other emissive Between these two low to the subthalamic region The third frontal convolution and its subjacent white matter are excluded.

Moutier in 1908 published an important monograph on aphasia from Marie's laboratory Dejerine took issue with Marie's view and especially insisted that the term anarthria should be used only for troubles of articulation (as in pseudobulbar palsy etc.)

Head, in 1910 began to devise new tests for aphasia as a result of his belief in Jackson's views of the subject He regrouped cases of aphasia as follows

1 Verbal aphasia defective word formation both in internal and external speech

2 Syntactic aphasia, want of coherence and a tendency to talk jargon

3 Nominal aphasia defective use of nouns both spoken and written

4 Semantic aphasia deficient comprehension of the full significance of words and phrases

Head introduced the term symbolic thinking and expression Head's contribution to the subject in his papers of 1920 and 1923 in Brain" was mostly in the nature of an analysis of what aphasia is from a psychologic point of view He described his cases as showing certain defects in what he called symbolic thinking and expression and pointed out that defects in these two spheres included not only imperfections in spoken and written language and in the understanding of them but also such things as the inability to recognize the difference in symbolic meaning of the big and the little hands of a clock the inability to recognize the difference between making a turn to the right and to the left and so on

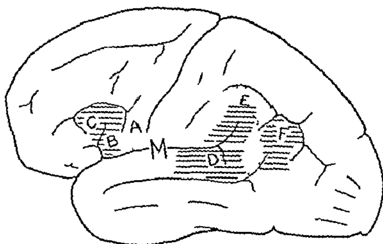


Fig 191.—The zone of language and the localization of the main types of aphasia A B C motor aphasia, characterized by aphemia D Temporal lobe aphasia characterized by word deafness anomia, jargon E Supra marginal gyrus aphasia characterized by global aphasia and apraxia F Angular gyrus aphasia, characterized by alexia M Mixed aphasia the common type of aphasia, characterized by aphemia, *agraphia, some alexia* with word deafness and marked hemiplegia

lay the island of Reil and therefore there were three possible kinds of aphasia The first was sensory with the lesion in the temporal lobe the second was motor with the lesion in the third frontal convolution and the third was a conduction aphasia with the lesion between these two centers

Wernicke's zone is the region including the posterior half of the first two temporal convolutions the angular gyrus the supramarginal gyrus and their subcortical areas

In 1906 Marie one of Broca's interns contributed a new theory to the discussion on aphasia His view in brief was that there was only one kind of aphasia the aphasia of Wernicke and that the motor aphasia of Broca is a combination of Wernicke's (sensory) aphasia with anarthria Anarthria he ascribed to a lesion of his lenticular zone which is a quadrilateral area defined anteriorly by a vertical plane passing through the anterior marginal fissure of the insula and posteriorly by a parallel plane through the posterior marginal fissure of the insula within it is bounded by the lateral ventricle and without by the surface of the insula. Above, it extends to the suprajacent convolutions, be-

Types of Aphasia.—Because the condition has not been fully understood and because various terminologies have been employed by different investigators it may be well to define briefly a few of the terms commonly encountered Cortical motor aphasia is the name sometimes given to a speech defect produced by a lesion in Broca's convolution Subcortical motor aphasia pure

motor aphasia and the pure word dumbness of Dejerine are terms used to describe a condition supposedly produced by interruption of nerve fibers which connect Broca s area and the center for articulation in the foot of the precentral convolution To the condition in which spontaneous speech is lost and the ability to repeat words is retained the name transcortical motor aphasia (Lichtheim's) is given This disturbance is caused by a cerebral lesion outside Broca s area, which interrupts the fibers passing to Broca s area from regions where word memories are aroused *Cortical sensory aphasia* is the disorder caused by abnormality in the cortex of the temporal lobe. The terms sub cortical sensory aphasia " Wernicke s pure word deafness and Dejerine s pure sensory aphasia are all used to describe functional separation of the sensory speech center from the auditory receptors by a lesion in the sub cortical nerve fibers Interruption of the fibers which connect Wernicke s zone with Broca s area (in the island of Reil for example) is known as *conduction aphasia* This does not destroy voluntary speech but produces paraphasia *i.e* skipping of words frequent repetition and confusion. "Dyslexia is the name applied to a condition in which the patient can only read a few words or sentences before he becomes fatigued and refuses to continue "Echolalia" signifies involuntary repetition of the last words spoken to the patient. Since a full description of all these types is impossible here the following discussion will include only motor and sensory aphasia

Motor aphasia is a condition in which a lesion in the speech center destroys the power to utter words which are in the patient s mind Its association with difficulty in reading depends on the previous mental habits of the individual. For instance the tendency to pronounce distinctly but silently each word that is read would doubtless lead to complete loss of the ability to read as well as to speak if a lesion developed in Broca s area Other variations in the clinical evidences of such lesions are probably to be explained by other mental habits Some individuals can normally remember words or figures only after seeing them, while in others retention is possible after they have been merely heard The great personal variation in the ability to form abstract propositions is sufficient to account for the various degrees of diminution in the power associated with lesions of similar situation and extent Because the few words which an aphasic patient can use are expletives and parts of the native language which have become automatic it has been suggested that the right hemisphere is responsible for their control. It is quite common for a patient to be able to use a few words of profanity such as Damn Oh Hell and so on, and it is well known that anyone who has acquired some facility in the use of a foreign language late in life may lose this entirely after becoming aphasic although he is still able to speak his native language The ability to solve simple arithmetic problems may be more or less affected (akalkulia)

In determining the location of the causative cerebral lesion it is first necessary as Kennedy has pointed out, to determine on which side of the brain the speech centers lie To do this it is essential to know whether the patient and also his stock are habitually right or left handed for heredity rather than use seems to determine whether the speech centers are on the right or left side of the brain The fact that the ability to write is often lost in aphasia is probably to be accounted for by involvement of the posterior end of the second frontal convolution by the lesion.

Perhaps the clearest conception of motor aphasia can be given by citing a typical case

Sir James Purves-Stewart in discussing Head s work described a condition in which all speech was suddenly lost, although the intelligence remained unimpaired. There was facial weakness on the right side. The patient was able to understand and execute all sorts of verbal commands, such as bending the thumb half way or straightening it out. The Babinski reaction was found on the right side No paralysis of arm or leg was discovered At autopsy there was a small lesion in the lower third of the left precentral gyrus due to embolic blocking of a small cortical arteriole This extended deeply into the operculum, but affected neither the insula nor the basal ganglia. Marie s "lenticular zone" was not involved. There was no other lesion elsewhere in the brain.

A somewhat atypical case mentioned by Bailey may also be of interest

A slight difficulty in reading was followed by inability to write a letter and later by definite aphasia, mainly of the motor type. The patient had great diffi-

culty in pronouncing words although she knew what she wanted to say Her comprehension of written speech was perfect and she could execute verbal and written commands easily The difficulty in reading and writing persisted although she could write her name There was some numbness in the right hand, and jacksonian fits involving the right face and tongue were associated with some residual weakness of the right lower side of the face and right hemihypesthesia with equivocal Babinski on the right side In this case the difficulty in reading was probably due to inability to say or write the words and not to inability to comprehend the meaning of the words—not a true alexia

A nodule of metastatic melanosarcoma (3×2 cm) was removed from the foot of the left second convolution at operation

"Sensory aphasia" is the term usually applied to inability to understand spoken or written language (word deafness word blindness alexia)

Word deafness is caused by a lesion of the posterior part of the left superior temporal convolution It is evidenced by inability to understand words which are heard by inability to repeat words and sometimes although not as a rule by loss of power to speak anything except jargon The patient is usually unaware of his errors of speech and is therefore not distressed by them as is the patient with motor aphasia Word deafness seems to be associated with some degree of mental impairment which may in certain instances arouse suspicion of insanity When the word deafness is not absolute the patient may understand an expected sentence from the doctor such as 'put out your tongue while he cannot carry out other spoken commands Gowers points out that expectancy seems to lower the resistance in certain nerve combinations just as it does so often in sleep Patients frequently have great difficulty in voluntarily naming an object which is held in front of them even when their normal vocabulary is large This so called *anomia* is not associated with loss of appreciation of the use of an object Sometimes a patient who cannot recollect a name after visual perception alone is able to do so when a second sense such as that of touch is called into play Another type of this indirect method of recollecting words is well illustrated by the author s experience On being asked what his telephone number was one patient said Olive 2–34–56–789 The number was Olive 2469 but it could be said only by means of gradual 'climbing up The same held true of the street address

For patients with word deafness the more automatic parts of speech, such as prepositions adjective etc , are easier to use than nouns Some individuals can say what they wish if they 'say it at once" At times words are uttered automatically as in the singing of a song Gowers suggests that when the left hemisphere is involved the automatic revival of words is probably made possible by the centers in the right side of the brain and he states that the slow recovery of the power of comprehension of spoken words is by the 're education' of the right hemisphere, since such regained power has been again lost in right sided disease"

Recovery from sensory aphasia seems easier than from motor aphasia.

Pure *word blindness (alexia)* which is produced by a lesion in the angular gyrus is not common The symptoms are inability to read print although it is clearly seen, and although the patient continues to write talk and understand spoken words well He can not copy satisfactorily Some suffer from hemianopsia and contralateral hemianesthesia or paresthesia There is seldom any motor weakness The intelligence is preserved

The most common type of aphasia is the *mixed* (frontolenticular lenticular zone aphasia) It is evidenced by total or marked loss of voluntary speech (aphemia) impairment of the ability to read difficult comprehension of spoken words and as a rule by marked hemiplegia without loss of sensation It results usually from hemorrhage from the branch of the middle cerebral artery which supplies the corpus striatum and internal capsule of the left side and involves the lenticular zone of Marie and some of the fibers from the frontal and temporal lobes

So called *global aphasia* which involves all parts of speech, is caused by a lesion of the left gyrus supramarginalis It is associated with apraxia or inability to perform certain acts where no paralysis prevents their execution According to Foix *apraxia* is of three kinds the motor which is usually unilateral right sided and renders the patient unable to imitate the voluntary movements necessary to perform such an act as brushing the hair when he is given the brush and asked to use it the ideational

(sometimes called *agnosia*) which seems to destroy the idea of how to perform an act alone although imitation is possible, and the ideomotor, which is a combination of these two and is characterized by loss of the idea of the act to be performed and by awkwardness in attempting to perform it

Examination of an Aphasic Patient.—In an aphasic patient the general neurologic examination is of great importance, because it often aids directly in determining whether the lesion is on the right or left side of the brain and whether it is situated in the frontal temporal parietal or occipital lobe In some individuals, exact localization of the abnormality depends entirely however on the type of speech disturbance. The following points are of great importance in the diagnosis of aphasia and should be carefully observed by the physician

Is the patient right or left handed, and is he of right or left handed stock?
How much voluntary speech is retained what are the defects in pronunciation and is the speech jargon?
If there is little or no voluntary speech is it possible to express ideas or emotions by pantomime or gesture?
Can the patient write voluntarily and to dictation?
Can he calculate or solve simple arithmetic problems?
Can he hum or sing a song?
Can he understand spoken language and obey simple commands, such as to bend the right thumb or to touch the right ear with the left thumb?
As commands become more complicated is it possible for the patient to obey them? For example, can he, on request, take your pen and pencil place the pencil on his table and return the pen to you?
Can he name a series of common objects (pen pencil, penny handkerchief notebook key box of matches the colors of different cards) which are placed in front of him and can he write the names of them as they are presented to him?
Does he appreciate their use?
Can he choose from a group of objects those for which you ask?
Can he correlate the printed name of an object with the object itself?
Does he understand the meaning of gestures? (Pretend you are going to hit him)
Can he read aloud and silently and can he repeat the substance of what he has read?

The degree of symbolic thinking and expression retained may be further tested by means of jig saw puzzles games of cards (bridge or poker) drawing both voluntarily and to command copying objects making a plan of a well known room telling time and placing the hands of a clock in certain positions at command

Treatment—In addition to removal of the cause of aphasia the treatment consists in reeducation Patient work under guidance often allows the subject to acquire a satisfactory vocabulary again Whether this is accomplished by vicarious activity of centers in the right side of the brain or not seems to make no difference in recovery of the function of speech Teachers accustomed to educate deaf and dumb children by the oral and lip reading methods are often very successful in such therapy

LEWIS STEVENSON

REFERENCE

Head Hughlings Jackson Lecture for 1920 Brain 1920 1923

AFFECTIONS OF THE BLOOD VESSELS OF THE BRAIN

Cerebral Arteriosclerosis.—Arteriosclerosis of the brain may be part of a generalized arteriosclerosis or a process limited to the cerebral vessels

Symptoms—The symptoms of arteriosclerosis of the brain are varied There may be mild dizziness or severe syncopal attacks occasional nausea or vomiting which may lead to the erroneous diagnosis of indigestion transitory paralysis of one side, or fleeting aphasia Multiple small foci of softening may lead to intellectual deterioration or even obvious dementia they often produce the syndrome of *pseudobulbar paralysis* with dysarthria small step gait emotional instability and salivary drooling

EPILEPSY may also be a symptom, in fact many cases of epilepsy coming on late in life are caused by cerebral arteriosclerosis Mild types of arteriosclerotic disease of the brain appear under the guise of *neurasthenia* There may be severe vertigo which resists treatment or occurs in episodes headache mild delirium disorientation inability to concentrate or a syndrome resembling Korsakoff s psychosis In all of these cases it is very important to look for changes in the retinal arteries Occasionally however even advanced arteriosclerosis of the brain may not give rise to symptoms during life and the patient may retain his full mental vigor

In most cases postmortem examination reveals atrophy of the convolutions thicken

ing of the meninges and cortical vessels and an increase in the glia The patient exhibits emotional instability, impairment of memory, and various phases of mental deterioration Some individuals become irritable, highly emotional suspicious, and slovenly, indeed the personality may completely change The writer has observed great sexual hyperactivity in a man of seventy five

There are special types of arteriosclerosis of the brain The arteriosclerotic process may involve either the system of short cortical vessels or the long medullary branches In the first instance, the surface of the brain assumes the appearance of beaten silver, in the second extensive areas of softening and cyst formation in the subcortical layers and in the basal ganglia are observed In the *presbyophrenia of Wernicke* there is a tendency to fabrication and disturbance in memory with preservation of thought and judgment The *Binswanger form of presenile dementia* is characterized by loss of memory and mental hebetude *Alzheimer's disease* by progressive dementia, aphasia and at times focal symptoms

Treatment—The treatment is largely prophylactic Avoidance of physical or mental overexertion, and the institution of rest cures at home or in a sanatorium provide psychic rest and physical relaxation Graduated exercises may be tried but should be so regulated that the patient can rest for part of the day In the severe types complete cessation of work may be necessary Patients should be warned against straining at stool Sexual activity must be limited. The diet need not be restricted to milk and vegetables, but excessive consumption of meat cannot be permitted Curtailment of the salt intake is desirable The meals ought to be small and taken with as little fluid as possible The patient should not be permitted to gain weight in fact should reduce slightly Alcohol coffee and tobacco should be limited Mineral oil or mild cathartics may be given to regulate the bowels Warm baths and other forms of hydrotherapy are beneficial particularly for patients with nervous symptoms Nauheim baths also are of service Cold baths should be avoided For the headache and vertigo which frequently are troublesome hot fomentations may be applied to the forehead and neck Mild massage is also of value The high frequency current has its uses.

Iodides which still play the chief role in the medical treatment, are said to delay the advance of the disease They may be administered in the form of sodium or potassium iodide (0 3 Gm three times a day after meals) Occasional doses of diuretin (0 5 Gm two or three times a day) may be of service Nitrites have been recommended to reduce hypertension In neurotic individuals, bromides seem to relieve the headache, vertigo insomnia, and excitement For arteriosclerotic epilepsy, phenobarbital (0 03 to 0 06 Gm twice a day) is a great aid for the insomnia either sodium amytal (0 09 to 0 18 Gm), pentobarbital (0 09 to 0 18 Gm) or seconal (0 09 to 0 18 Gm) may be given before retiring Antineuralgic remedies may be employed for headache Treatment should also be devised for the accompanying nephritis and hypertension

Circulatory Changes in the Brain—Our knowledge of circulatory changes in the brain is incomplete Data are for the most part obtained during fainting spells or from plethoric patients Experiments have demonstrated however that a sudden, large loss of blood or the acute shutting off of the cerebral circulation usually gives rise to convulsions and coma In dogs simultaneous ligation of the carotid and vertebral arteries produces idiocy owing to definite changes in the nerve cells of the cortex These have been ascribed to anoxia

Anemia of the brain becomes manifest after severe hemorrhage or the aspiration of a large quantity of ascitic fluid in acute cardiac weakness and in spasm of the cerebral blood vessels The best example of an acute cerebral anemia is that resulting from the rupture of an ectopic pregnancy The face and mucous membranes are pale, the patient complains of blackness before the eyes, there is clouding of consciousness, and the gait becomes unsteady The patient experiences buzzing in the ears and nausea frequently vomits is apathetic and drowsy The pupils are small The syndrome resembles sleep Great loss of blood is followed by coma marked dilatation of the pupils and frequent convulsions

Mild hemorrhage simply produces "faintness The patient loses his senses," yawns a

great deal, and exhibits cold perspiration and pallor of the skin and mucous membranes. The pulse becomes rapid the respiration sighing and irregular There are no convulsions The syncope may last from a few minutes to an hour Consciousness returns when the patient is made to lie down

FAINTING may result from fear sorrow the sight of blood or severe pain Neuropathic individuals faint easily There may be a hereditary predisposition to syncope

CHRONIC ANEMIA is associated with chlor anemia pernicious anemia leukemia bleeding hemorrhoids and other causes of blood loss It is manifested by pressure in the head drowsiness apathy, vertigo tendency to faintness impairment of memory and Korsakoff like phenomena In some cases a change may be noted in the circulation of the retinal vessels The symptoms are usually worse when the patient is erect The delirium of inanition may be due to cerebral anemia. The mental symptoms in these cases are now ascribed to avitaminosis Severe diarrhea may evoke similar symptoms (hydrencephaloid state of Marshall Hall) A general spasm in the cerebral vessels may result in cerebral anemia That the cerebral blood vessels have a definite vasomotor innervation has been recently proved by the work of Forbes and Wolff Cobb and Finesinger

PROGNOSIS—Mild attacks of cerebral anemia are rarely dangerous. Severe hemorrhage with repeated convulsions may prove fatal Dilatation and fixation of the pupils is usually an ominous sign Primary optic atrophy aphasia or hemianopsia may follow severe hemorrhage

TREATMENT—In the acute cases after the cessation of the hemorrhage the patient is placed in the recumbent position The extremities are bandaged tightly and elevated in order to supply blood to the heart. Heat is applied Stimulants such as caffeine or hot coffee may be administered Amyl nitrite is sometimes of value Artificial respiration transfusion or saline infusions are powerful aids

Hyperemia—Cerebral hyperemia may be active or passive The possibility of permanent overfilling of the brain with arterial blood is remote but transitory hyperemia may occur in plethoric individuals with the apoplectic habitus It is manifested by ready suffusion of the face after meals or after exertion, and is often associated with elevation of blood pressure and cerebral congestion The patient has a subjective sense of warmth exhibits redness of the face and speaks of throbbing of the temples spots before the eyes headache and vertigo There is usually slight clouding of consciousness in the more severe forms of hyperemia there may be confusion and even manic excitement. Apoplectiform seizures with transitory paralysis, may occur

Amyl nitrite has been known to produce a temporary aphasia owing to cerebral congestion and disturbed vasomotor tone A tendency to congestion of the brain is frequently observed in psychoneurotics Onanism may be an etiologic factor in such cases Oppenheim has observed the association of cerebral congestive symptoms with stubborn constipation Among the other causes of cerebral hyperemia may be mentioned the contraction of the peripheral blood vessels after a cold bath and the suppression of menses The exacerbation of migraine with each menstrual period may be due to cerebral congestion or hydremia. Augmentation of the blood supply to the head may also result from dilatation of the cerebral blood vessels

PASSIVE HYPEREMIA is usually a chronic condition due to interference with the venous return from the head by tumors in the neck thyroid enlargement compression of the superior vena cava by mediastinal tumors cardiac decompensation or emphysema Pulmonary abnormalities which increase the intrabronchial pressure may also serve as etiologic factors by interfering with the return flow of blood to the thorax

SYMPTOMS—The symptoms are drowsiness headache which is aggravated by coughing vertigo and confusion. They become worse when the patient lies down Cyanosis of the mucous membranes and of the face is usually present

PROGNOSIS—The prognosis of simple congestion of the brain is unfavorable only if there is antecedent organic disease of the heart or blood vessels The apoplectiform habitus predisposes to cerebral hemorrhage

TREATMENT—The treatment is largely symptomatic it consists of catharsis and the

relief of headache and insomnia by the administration of mild narcotics (bromides and chloral) The effects of lesions of the superior mediastinum (substernal struma) may be ameliorated by surgical interference All forms of physical and mental exertion are to be avoided, the use of strong coffee and tea is best interdicted alcohol should not be taken

During the attack the patient must be made to sit up The room should not be too warm Application of mustard to the neck chest or lower extremities frequently gives relief In severe cases particularly in plethoric individuals venesection vigorous catharsis and hot foot baths are necessary For cardiac decompensation it may be desirable to give digitalis

Cerebral edema is not a clinical entity but is associated with serous meningitis In many cases of cerebral congestion the blood vesesls are distended and the brain is exceedingly moist This picture is often seen in uremia and in alcoholic intoxication it may occur as a sequel of trauma It sometimes is secondary to the formation of tumors or abscesses and renders the brain anemic and glistening A moderate degree of internal hydrocephalus is usually present. The symptoms are those of the underlying condition Uremic paralysis and convulsions have been ascribed to this edema of the brain

Cerebral Hemorrhage—*Incidence*—Hemorrhage into the brain is one of the *commonest cerebral accidents Although* it usually occurs in later life (after the age of forty) it can occur at any age It is more frequent in men than in women The hemorrhage is almost always the result of vascular disease—particularly atherosclerosis and usually follows rupture of some of the branches of the circle of Willis—especially the branches of the sylvian artery (middle cerebral)

Etiology—The causes of vascular disease of the brain are manifold among the most frequent are hypertension advancing age intoxications (alcohol lead tobacco diabetes gout), and infections such as syphilis In lues thrombosis occurs more often than hemorrhage Acute infectious diseases (typhus and scarlet fever) occasionally give rise to cerebral bleeding At times the cerebral hemorrhage is an incident in hemorrhagic diathesis (purpura, pernicious anemia and leukemia) Chronic glomerulonephritis with its associated hypertension increases the danger of bleeding There may be a familial tendency to cerebral hemorrhage

Bollinger described a clinical entity which he designated traumatic late apoplexy' This type of apoplexy follows in the wake of trauma and usually makes its appearance several days or weeks after the accident Bollinger postulated primary circulatory disturbances alteration of the tissues and subsequent hemorrhage into the softened area

The immediate cause of hemorrhage is a rapid rise in blood pressure This may occur as a result of severe muscular exertion coughing sneezing straining at stool coitus parturition or vomiting In children whooping cough, severe mental excitement and fear may be the precipitating factors Trauma may serve as an exciting cause in the presence of damaged vessels According to Volkmann a pressure fourteen times the normal is required to rupture the healthy carotid artery

Morbid Anatomy—Certain areas of the brain exhibit a predilection for hemorrhage *i e* the region of the basal ganglia (including the corpus striatum optic thalamus and the adjacent part of the capsule) the centrum semiovale the cortex and the pons Cerebellar hemorrhage is rare

Miliary aneurysms seldom develop in the arteries of the basal ganglia but sclerosis *may become advanced* The lenticulostriate and the lenticulo optic branches of the sylvian artery are the vessels most commonly involved The lesion may attain a diameter of 1 mm At first only the muscular coat atrophies later all the coats undergo degeneration This gives rise to dilatation of the vessel wall with consequent imminent danger of hemorrhage *

The size of the hemorrhage varies The escaping blood may plough through the brain tissue and make its way into the ventricles The largest foci are usually found in the basal ganglia and centrum semiovale those in the cortex and pons are as a rule much smaller Their color and nature vary

* Rosenblath and others have called into question the significance of miliary aneurysms in the genesis of cerebral hemorrhage They maintain that hemorrhage always occurs into a preexisting area of softening

with the age of the hemorrhage when fresh they have the color and consistency of recently coagulated blood later they may turn brownish black, brown or even yellow after the fifth week the yellowish color becomes more and more evident

At least four weeks are necessary for the formation of an apoplectic cyst. In the adjacent brain substance, proliferation of the glia precedes the formation of true connective tissue The contents of the focus are slowly absorbed and only a cavity remains This is later filled with yellowish fluid When the hemorrhage is extensive and causes immediate death, the convolutions are found flattened and the sulci narrowed

Symptoms—APOPLECTIC SEIZURE—The immediate sequel of cerebral hemorrhage is the apoplectic seizure Most patients exhibit *premonitory symptoms* such as dizziness a sense of pressure in the head hemiparesthesia anxiety confusion and disturbances of speech, others give a history of high blood pressure arteriosclerosis and pathologic urinary changes But the apoplectic seizure may occur suddenly in an individual who is in apparently perfect health Epistaxis or retinal hemorrhage sometimes precedes the acute manifestation *At the onset* the patient may suddenly fall to the ground and rapidly become unconscious (fulminating apoplexy), or may suffer merely a clouding of consciousness There may be only a transitory vertigo The clinical variations depend upon the size rapidity, and site of the hemorrhage Bleeding into the cerebellum and pons is less frequently associated with disturbances in consciousness

During the height of the attack the patient is comatose and cannot be roused The face is flushed and puffy the pupils do not react to light, they may be normal in size or dilated the corneal reflexes are abolished bilaterally the extremities are limp and both deep and superficial reflexes are absent The pulse is full and bounding at times rapid Breathing is slow deep and often stertorous because respiration sets the flabby palate and vocal cords in vibration at times it is of the Cheyne Stokes type The cheeks are often puffed out more so on the paralyzed side The patient cannot swallow even fluids There is incontinence of urine and feces occasionally retention occurs The urine contains albumin and often sugar (postapoplectic albuminuria and glycosuria) There may be generalized or unilateral convulsions Fever usually develops soon after the attack and if high, is of serious import

The apoplectic seizure may last from several hours to several days The causes of the coma are the circulatory disturbance in the brain the pressure of the exudate and diaschisis

In many cases there is conjugate deviation of the eyes A mild papilledema may be observed usually on the side of the lesion. If death does not result the patient gradually regains consciousness and exhibits a hemiplegia As he emerges from coma the reflexes return and, in spite of continued somnolence swallowing becomes possible There is some return of active motion Asymmetry of the face with sagging of the angle of the mouth on the affected side is noticeable the palpebral fissure is wider than normal the nasolabial fold is less marked and the patient drools on the paralyzed side The muscle tonus in the limbs is increased Cremasteric and abdominal reflexes are absent on the paralyzed side The Babinski sign is positive and the Oppenheim Rossolimo and Mendel reflexes as well * In respiration the involved side of the chest lags and the homolateral diaphragm functions poorly

If there is conjugate deviation of the eyes and the patient is in coma the hemorrhage is usually situated on the side toward which the head and eyes are directed Patient looks at his lesion' O Foerster found a number of oculogyric centers in the brain frontal parietal and temporal in location When these are irritated the patient looks away from his lesion when they are paralyzed the intact centers in the opposite hemisphere cause him to look at his lesion

Hemiplegia is often accompanied by vasomotor disturbances such as edema of the involved hand The pain which may be felt on the paralyzed side is either arthritic or central (thalamic) in genesis In conditions complicated by heart disease or nephritis

* The writer described the abolition of the corneal reflex on the hemiplegic side and emphasized the value of this sign in the diagnosis of vascular accidents of the brain

the edema may be more marked on the affected side When there has been no antecedent apoplectic manifestation, paralysis may be the first symptom The patient notes that he cannot hold or grasp things so well as previously or that his leg gives way under him

HEMIPLEGIA —The typical result of the apoplectic seizure is hemiplegia, i e, paralysis of the face tongue, arm, and leg, on one side of the body For a short period after seizure sensation is disturbed that associated with the posterior column i e the perception of vibration joint movements, and two point discrimination, more markedly than pain and temperature perception Speech is dysarthric and indistinct If the internal capsule is directly involved in the hemorrhage and more or less destroyed hemiplegia remains as a direct focal symptom Later on the picture changes somewhat There is marked increase of the deep reflexes on the paralyzed side and frequently a tendency to ankle clonus After several weeks a certain amount of mobility returns on the involved side owing to the functioning of accessory motor pathways The arm usually remains paretic for a longer period the leg is held in extension the arm may exhibit some return of power more proximally than distally The extensors of the hand and fingers seem to be seriously involved, those of the thumb most severely The flexors of the knee and the extensors of the feet and toes are very apt to remain permanently impaired Hemiplegic patients regain power slowly and usually can walk after six to eight weeks

After a time the *muscle tonus* in the affected limbs increases and contractures develop, especially in the arm The upper arm is adducted the forearm flexed at an angle, the hand pronated and flexed, and the fingers tensely flexed The leg usually becomes fixed in extension The contraction of the gastrocnemius group leads to the formation of pes equinus or pes equinovarus and gives rise to considerable difficulty in walking The patient therefore, supports himself on his sound leg and by circumduction lifts the paralyzed leg from the ground and swings it through an arc He thus avoids scraping the floor in walking Sometimes the paralysis remains flaccid this condition according to Oppenheim, results from very extensive disease of both the motor and sensory pathways In the author s experience the incidence of rigidity seems to depend on the proximity of the lesion to the basal ganglia Fulton ascribes the rigidity to a lesion of the fibers from the premotor zone The musculature usually remains intact, but there may be some atrophy from inactivity There are however, no changes in electric irritability aside from altered chronaxie

If the hemorrhage extends to the posterior limb of the internal capsule or into the optic thalamus there occurs in addition to the hemiplegia a *hemianesthesia* All forms of sensation are diminished or lost, the sense of touch being most involved The sensory changes may be limited to the distal parts of the extremities Hemiataxia may result from loss of postural sensation and is usually accompanied by astereognosis and tabetic athetosis

A certain amount of *mental disturbance* follows in the wake of cerebral hemorrhage. There may be diminution of intelligence, irritability, and disturbance of memory Actual dementia develops only when cerebral softening takes place owing to generalized atherosclerosis or lues The involved limbs may be unduly warm or cold and cyanotic Trophic changes in the joints have been described (Charcot) In right handed individuals, if the hemorrhage involves the subcortical pathways of association on the left side there may be aphasia The more extensive the hemorrhage and the more it damages the speech center the more permanent the aphasia When the hemorrhage bursts into the ventricles and reaches all chambers of the brain as it occasionally does, the paralysis spreads to all the extremities Convulsions may ensue, but more often generalized rigidity of one or both sides develops The pulse is slowed The temperature falls There are marked respiratory difficulties Lumbar puncture releases bloody fluid Such a hemocephalus usually proves fatal within twenty four hours

Hemorrhage into the pons and medulla may be bilateral or unilateral it may involve the tegmentum Clinically bleeding into the pons may be manifested only by vertigo The most common objective sign is the alternating hemiplegia (homolateral

cranial nerve palsy, contralateral hemiplegia) The paralysis is usually associated with disturbances in articulation and deglutition. The pupils are usually narrow often fixed The third cranial nerve, the motor fifth and the sensory fifth may also be involved owing to extension of the lesion upward in the brain stem General convulsions may occur Opisthotonos is not uncommon Respiration is often seriously disturbed Hemorrhage into the pons may evoke symptoms of acute bulbar paralysis but these are much more frequently observed in apoplexy of the medulla Cerebellar hemorrhage gives rise to cerebellar ataxia vertigo and vomiting

Differential Diagnosis—The differential diagnosis of apoplexy is of great importance The condition must be distinguished from simple fainting epilepsy uremia hysteria and the coma caused by intoxication *Simple fainting* can easily be distinguished by the absence of a profound loss of consciousness and by its short duration The pulse is usually rapid and feeble The fainting person is pale, but not comatose The *epileptic seizure* is indicated by tongue bite scarring of the tongue from previous seizures and the absence of hemiplegic phenomena Epilepsy is much more common in younger individuals *Attacks of hysteria* are easily excluded by retention of the pupillary reflexes and the presence of normal deep reflexes. The general attitude of the patient is quite different from that of the apoplectic individual. The face and tongue are rarely involved The Babinski sign is absent Abdominal reflexes are retained The hysteric hemiplegia is also frequently accompanied by a characteristic hemianesthesia The condition yields readily to psychotherapy *Uremic coma* can be differentiated by the presence of albumin and casts in the urine the demonstration of edema or albuminuric retinitis the history of headache vomiting and asthmatic attacks and the study of the blood chemistry *Diabetic coma* can also be ruled out by examination of the urine and the incidence of acidosis (acetone odor in the breath low CO_2 content of the blood) *Alcoholic coma* can be detected by the odor of alcohol the tendency to delirium and motor restlessness Morphine intoxication renders the pupils typically miotic *Acute hemorrhagic encephalitis* is also characterized by clouding of consciousness but is usually preceded by headache and fever The coma is less profound and the reflexes are often retained

In apoplexy not accompanied by profound coma the corneal reflex is diminished or abolished on the side of the hemiplegia. This unilateral diminution or abolition of the reflex is often of great value in distinguishing the coma due to apoplexy from that dependent on other causes The differentiation of cerebral hemorrhage from softening due to *embolism* or *thrombosis* is not always easy Hemorrhage is rare before forty" embolism is most common in children, and thrombosis usually occurs in middle life The presence of cardiac lesions suggests embolism arteriosclerosis indicates thrombosis and so also does syphilitic infection Simultaneous hypertrophy of the left ventricle and nephritis would point to hemorrhage The history of recent rheumatism even without endocarditis suggests embolism Redness and puffiness of the face and a full strong pulse should arouse suspicion of hemorrhage Most apoplectic patients exhibit hypertension The coma of hemorrhage is deep and persistent Premonitory symptoms such as paresthesiae transitory weakness of one side and intermittent disturbances in speech favor a diagnosis of softening or thrombosis With embolism preliminary symptoms are unusual Repetition of the vascular injury suggests embolism The absence of loss of consciousness and the appearance of symptoms indicative of an extensive lesion point to softening The incidence of phenomena of *motor irritation* especially of jacksonian seizures is higher in embolism and thrombosis

The symptoms of *cerebral tumor* may be simulated by *focal signs owing to the presence of an arteriosclerotic cyst*

Hemorrhage into a hitherto *latent neoplasm* may simulate thrombosis The onset of a metastatic neoplasm of the brain may resemble a vascular accident. There have been reported cases of transitory hemiplegia resulting from *cerebral angiospasm* The condition is allied to intermittent claudication of the lower extremities These vascular crises" as they have been termed by Pal are particularly common in smokers

Prognosis—The apoplexy may rapidly prove fatal especially in those cases in which the hemorrhage is extensive and perforates into the ventricle If the coma persists more than twenty four hours or constantly deepens there is grave danger to life. A steady *fall or an unusual rise in* temperature is also of serious import *Decubitus acutus* and Cheyne Stokes breathing are unfavorable manifestations Hemorrhage into the pons and medulla is often fatal Secondary aspiration or hypostatic pneumonia is a frequent cause of death After the occurrence of hemiplegia the symptoms diminish in severity the less complete the apoplectic attack the better is the outlook although a small hemorrhage in the region of the motor tract may evoke permanent unilateral paralysis Careful observation of the symptoms during the first week is necessary If the hemiplegia persists unchanged for a month or more it is *indicative of invasion of the motor* tract and recovery is unlikely If on the other hand muscular power returns somewhat during the first few days the prognosis is much better The character of the reflexes does not seem to be significant The presence of contractures is of serious import Most aphasias associated with hemiplegia seem to improve although frequently only after considerable time and then only partially Hemianopsia is also apt to be permanent The rapid subsidence of paralysis within a few days particularly in a young adult without hypertension suggests very strongly that the attack may be the first episode in general paresis This need disturb neither the intelligence pupillary reaction nor speech but the serologic findings characteristic of syphilis can usually be demonstrated

It may take the individual three or four months to regain the power of locomotion and then only with the patient help of the physician and family The prognosis for patients who have sustained a cerebral hemorrhage is uncertain because the etiologic substratum remains Fifteen to twenty years however may intervene between the first apoplectic attack and the one which causes death

Treatment—The treatment is *first prophylactic* *i e* that of the underlying vascular disease The patient should avoid liquor and tobacco and if adipose receive a diet carefully regulated to allow reduction of weight For the existing arteriosclerosis iodides (potassium or sodium iodide 0 3 to 0 9 Gm) are useful even in the nonsyphilitic cases Some observers advise reduction of the calcium intake while others favor the administration of milk About the need for restriction of salt and purines there seems to be general agreement Highly seasoned foods are undesirable. The patient should be instructed to avoid everything that suddenly elevates the blood pressure *i e* straining at stool sexual intercourse, the carrying of heavy weights undue physical exertion, and mental excitement A sojourn in a warm climate is often helpful

During the acute apoplectic attack the following therapy may be employed the patient should be put to bed with the head elevated If he has fallen to the ground the clothing around the neck must be loosened *Difficulty in swallowing contraindicates the* administration of nourishment by mouth An enema may be given When the face is puffy the pulse full and strong and there is reason to suspect hemorrhage venesection is advisable It should be employed only for plethoric individuals not for patients who seem asthenic or arouse suspicion of thrombosis Usually 250 to 300 cc of blood are removed No attempt should be made to arouse the patient For those with stertorous breathing the prone position is better If the tongue tends to fall back into the throat it should be held forward Attempts to treat the hemorrhage surgically have produced no striking results * If the diagnosis of hemorrhage can be made with reasonable certainty an ice bag may be placed over the site of the lesion Unless there is special need it is best during the first few days to avoid medication For restlessness bromides and chloral may be tried If there is much headache or sleeplessness an opiate or some other mild soporific should be administered If there is reason to suspect lues bismuth and salvarsan must be administered The attendant should guard against the development of decubitus The tendency of pulmonary congestion should be counteracted by frequent shifting of the patient from side to side

* In recent years there have been isolated reports of cases of improvement following surgical intervention

Treatment of the hemiplegia itself includes general massage of the paralyzed limbs and passive exercise In order to avoid contractures and changes in the joints such therapy may be instituted in the second week of illness After two or three weeks electric treatment (mild faradic current) may be employed The electric stimulation is best applied to the antagonists of the contracted muscles several times daily for four or five weeks At times surgical measures such as tenotomy and muscle transplantation may have to be employed The patient should make no effort to walk for three weeks and even then should spend the major part of the day in a bed Movements of locomotion may be carried out while he is sitting in a chair or lying down. If dependent limbs are cold and cyanotic support is helpful

Massage and passive motion should be continued for some time Aphasia requires adequate reeducation Warm baths are frequently useful The patient should be instructed to lead a more or less sedentary life in order to avoid further vascular accidents

Cerebral Softening (*Encephalomalacia*) —*Etiology*—Softening of the brain is caused by occlusion of an artery with resulting tissue ischemia and degeneration of the area of the brain deprived of nourishment Blocking of the vessel may follow either embolism or thrombosis *Embolism* takes place in chronic valvular disease (particularly in mitral stenosis) or in the auricular thrombosis *consequent upon dilatation of the* heart Occasionally the embolus originates in the aorta and in chronic suppuration of the lung it may come from the pulmonary veins Sometimes tumors of the heart lungs or other organs give rise to metastatic occlusion of the cerebral blood vessels The embolus may also be derived from a thrombus in one of the larger cerebral blood vessels

Thrombosis of the cerebral blood vessels is usually the result of arteriosclerosis or specific endarteritis Disease of the blood vessels may be produced by chronic intoxications (lead tobacco etc) or may be a result of hereditary weakness of the arterial tree Oppenheim thought that those psychoneuroses which were associated with symptoms referable to the cardiovascular apparatus often led to atherosclerosis early in life Laborers are also particularly prone to cerebral vascular disease

Certain diseases which increase the coagulability of the blood may give rise to thrombosis although the vessel walls are normal In this category are included infectious diseases (typhus scarlet fever polycythemia) and the puerperal state. Thrombosis is said to be more common in individuals with cardiac weakness owing to the circulatory retardation Chloranemia and leukemia may also be contributing causes, the former probably on account of the associated hypoplasia of the cardiovascular system Carbon monoxide poisoning often evokes softening particularly in the lenticular nucleus In some cases of tuberculous meningitis thrombosis induced by proliferative vascular changes has been observed Both embolism and thrombosis occur as the result of some precipitating factor such as fear excitement physical exertion or parturition The embolus usually remains fixed at the bifurcation of large vessels into smaller branches.

Morbid Anatomy—The sylvian artery (middle cerebral) and its branches especially on the left side, are most frequently involved the left vertebral artery is also occasionally affected Thrombosis occurs principally in the large vessels at the base of the brain Embolism may lead to secondary clotting of the blood in the neighboring vessels Occasionally there may be absorption or recanalization of the thrombus In cases of endarteritis the entire lumen of the vessel may be obliterated over a large area. The vessels descending from the cortex into the brain substance and white matter are usually end arteries In the cortex of the brain collateral circulation is more readily established than in the brain stem Occlusion of the sylvian artery therefore may not result in softening of the cortex but the deeper structures may be the seat of extensive degeneration According to Monakow occlusion of the main trunk of the middle cerebral (sylvian) artery leads to softening of the entire lenticular nucleus the anterior part of the optic thalamus the subthalamic region the motor area the island of Reil and the third frontal convolution Occlusion of the posterior cerebral

artery evokes softening of the occipital lobe the calcarine area the cuneus and the posterior part of the optic thalamus Occlusion of the anterior cerebral artery leads to softening in the frontal zone and along the longitudinal sulcus including the paracentral lobule

Softening may be found in all parts of the brain but most often in the cortex The caudate nucleus and putamen are also frequently affected thrombotic lesions are rare in the cerebellum The process of softening does not occur immediately upon occlusion of the vessel but may be delayed two or three days As soon as the brain assumes the characteristic consistency serous infiltration of the involved area takes place rapidly

Softening is of three types—red, yellow, and white, the color depends on the blood content of the tissues Red softening is particularly common in the cortex owing to its rich blood supply, it may also be frequently observed in the central gray matter near the aqueduct of Sylvius After a few weeks fatty changes in the diseased tissues and degeneration of the blood pigment render these red softened lesions yellowish in color In the white matter the softening usually assumes a whitish or bluish white color, in such areas we find droplets of myelin, detritus and granular cells The presence of these elements distinguishes true softening from *postmortem* maceration

After absorption of the degenerated material a cyst remains at times we find scarring This is particularly noticeable in the cortex which may become 'mouse eaten in appearance The size of the softened areas varies from that of a pin head to that of a fist An entire hemisphere may undergo softening for example after thrombosis of the carotid artery At times cerebral embolism may be associated with embolism of the central artery of the retina

Embolism occurs most often in young adults while thrombosis exclusive of the syphilitic type is seen chiefly in old people

The thrombosis involving the basal ganglia chiefly the lenticular nucleus is described as the lacunar type and leads to a clinical syndrome of paralysis agitans

Symptoms—In cases with large areas of softening particularly those due to embolism the *onset* is apoplectiform Embolism and thrombosis of the smaller vessels may occur without loss of consciousness If consciousness is lost the coma is not profound and is shorter in duration than that produced by hemorrhage It may be followed after several days by a rise in temperature, and in septic conditions by chills and fever Embolism of a large trunk always gives rise to loss of consciousness owing to mechanical injury to the brain or diaschisis The vascular occlusion may also be initiated by a convulsion Vomiting is a frequent symptom, occasionally there may be considerable prostration and mild delirium

Thrombosis of the principal vessels may also begin with apoplectiform symptoms but the loss of consciousness is usually less profound At times the paralysis develops very quickly There may be only a period of transitory confusion or mild disturbance of cerebration In some instances the patient complains simply of headache and vertigo In cases of embolism there are no premonitory symptoms while in thrombosis these are usually present and vary with the extent of the underlying arteriosclerosis The prodromata include pressure in the head, headache intensified by coughing sneezing straining at stool, or lying down as well as disturbances in memory and intelligence mild confusion and excitement or transitory aphasia Many patients suffer from sleeplessness exhaustion loss of interest and ambition emotional dulness irritability tendency to weep transitory paresthesiae and paralysis

The characteristic *result of cerebral softening* is the *hemiplegia* which is often progressive The mild hemiparesis is often followed by increasing weakness At first only one limb may be involved later the entire side is implicated In right handed individuals the motor phenomena are associated with aphasia When the area of softening is very circumscribed either a monoplegia with aphasia aphasia alone or hemianopsia ensues Indirect local signs may result from diaschisis * In such cases the paralysis may be an indirect symptom and the motor phe

* Diaschisis is a term suggested by Monakow for the mechanism which gives rise to transitory symptoms of brain disease owing to radiation of the insult from the focus involved to adjacent areas of the brain

nomena may disappear Hemianesthesia may accompany the hemiplegia exist alone or be associated with hemiataxia The hemiplegia may disappear owing to the establishment of a collateral circulation or the relaxation of angiospasm

Occlusion of the internal carotid especially if the anterior cerebral and the sylvian artery are involved evokes very extensive softening with hemiplegia and profound coma It leads rapidly to death Occlusion of the main branch of the sylvian artery causes hemiplegia with permanent or transitory hemianesthesia and aphasia if it occurs *on the left side in right handed individuals* When the plugging process involves only the branches the symptoms vary according to the area involved Occlusion of the first branch of the sylvian artery on the left side gives rise to motor aphasia with facial lingual and sometimes brachial paralysis, that of the second branch to hemiplegia or faciobrachial paralysis that of the third and fourth branches (which supply the lower parietal and upper temporal lobe) to alexia and word deafness The latter is especially noticeable after occlusion of the fifth branch Embolism or thrombosis of the anterior cerebral artery is followed by paralysis of the leg and psychic disturbances (akinesis) * Occlusion of the arteries supplying the white matter gives rise to hemiplegia and hemianesthesia Unilateral softening of the basal ganglia may evoke symptoms of motor irritation and all kinds of sensory abnormalities When the lesions are bilateral articulation and deglutition may be disturbed loss of mimetic display hyperemotionalism and bladder symptoms become evident (basal ganglion type of pseudobulbar palsy) In such cases phenomena referable to the pyramidal tract are not observed

Occlusion of the posterior cerebral arteries usually leads to hemianesthesia and hemianopsia. There are usually premonitory symptoms such as dizziness mental aberration headache transitory hemianopsia and other visual disturbances With the acute apoplexy there may be hemiplegia with convulsive manifestations After recession of the general symptoms the hemiplegia also disappears but the characteristic hemianopsia remains

Thrombosis of the basilar or vertebral artery commonly leads to acute bulbar paralysis A fairly typical symptom complex is engendered by thrombosis of the posterior inferior cerebellar artery (a branch of the vertebral) It frequently has an anomalous distribution but its blocking gives rise to a rather characteristic syndrome. In some cases death with bulbar symptoms ensues rapidly but if the patient survives the initial stage he exhibits a crossed sensory paralysis (homolateral involvement of the sensory *fifth and contralateral involvement of* pain and temperature senses) with ipsolateral ataxia of cerebellar type The innervation of the vagus and glossopharyngeus is also so disturbed that dysarthria dysphonia and difficulty in deglutition occur Sympathetic phenomena (Horner syndrome) also appear on the side of the lesion

Sometimes in cases of arteriosclerosis a number of small areas may undergo softening although there has been no major apoplectic seizure In these cases we find disturbances in intelligence bulbar speech spasmodic outbursts of laughing and crying and bladder symptoms (pseudobulbar palsy) Such softening when fully developed produces the syndrome of amnesia and aphasia which may go on to true senile dementia.

Diagnosis—If the symptoms (aphasia or monoplegia) point to a focal cerebral lesion and there is no history of trauma they are probably due to softening The differentiation of softening of the brain from *tumor* may be very difficult and can be made only after prolonged observation In most cases of cerebral softening evidences of increased intracranial pressure are lacking There is no papilledema slowing of the pulse or vomiting except in cases of thrombosis of the basilar artery † *Localized atrophies* of the brain occurring in advanced age may simulate softening but give rise to more profound coma and much more mental disturbance *Alzheimer s disease* must also be eliminated Many cases of softening of the

* Akinesis denotes an inhibition of psychomotor reactions i e disinclination to execute voluntary acts

† Within recent years the procedure of encephalography has become an important and valuable aid in distinguishing vascular from neoplastic lesions of the brain

brain without focal symptoms appear under the guise of *neurasthenia* The patients complain of headache vertigo prostration, and insomnia The constancy of the symptoms the absence of a neuropathic history and the signs of vascular disease especially in the retina will help to clarify the diagnosis Occasionally hemiplegia occurs in individuals in whose brain no changes can be found at postmortem examination This has been observed in *tuberculosis alcoholic intoxication uremia diabetes* and *lead poisoning* It is particularly difficult to distinguish uremic hemiplegia from that due to cerebral thrombosis although the former is more apt to be transitory Similar evanescent hemiplegias which may occur in the course of *pneumonia* or *allergic states* have been ascribed to edema of the brain or mild meningitic changes *Diabetes* may also be complicated by transitory hemiplegia

Prognosis —Death is less apt to occur in these cases than in cerebral hemorrhage Jones reports that death occurred in 30 per cent of a series of patients with cerebral hemorrhage in 15 per cent of those with thrombosis and in only 7 5 per cent of those with embolism Thrombosis of the basilar and carotid arteries is usually fatal The duration of the loss of consciousness is less significant than its profundity The general condition of the patient including that of the heart is important Those who suffer from localized softening may live for years If the paralytic symptoms do not improve within three or four weeks the ultimate prognosis is poor

Treatment —The treatment is first prophylactic *i e* that of the underlying arteriosclerosis Venesection is not necessary in cases of softening For the attack itself the treatment is with some modifications that of hemorrhage. For cardiac weakness stimulants may be given When there is reason to suspect a syphilitic origin of the vascular process bismuth and iodides should be administered at once and promptly followed by arsenotherapy The treatment of the paralysis has already been discussed

Intracranial Aneurysms —*Etiology* —Syphilis is rarely the cause of intracranial aneurysms They are the result of embolism of the vessel wall in infectious endocarditis or of cerebral atherosclerosis they may be congenital In the latter case there is frequently evidence of the constitutional dyscrasia known as status thymicolymphaticus '

Morbid Anatomy —The aneurysm may be of the miliary type or may involve the larger vessels Aneurysmal dilatation is more frequent in the cerebral vessels than in the other arteries of the body with the exception of the aorta The vessels most commonly involved are the arteries at the base of the brain or their branches before they penetrate the substance of the brain The lesions are frequently multiple and are usually sacculated. Their size varies from that of a pea to that of an egg They are more frequent on the left side The adjacent parts of the brain are usually compressed and may undergo atrophy or softening

The aneursyms usually develop in blood vessels which have lost their contractile substance in a circumscribed area Aneurysms of the cerebral vessels are more common in early and middle life Trauma has been said to be an etiologic factor There may be considerable softening around the sac only a small slit demonstrable in the vessel wall may indicate the site of rupture

Symptoms —The aneurysm may evoke no symptoms, or it may rupture spontaneously and lead to death There may be signs of mild cerebral hemorrhage or of fulminating apoplexy owing to rupture into the ventricles The site of perforation may be so small that there is only slow oozing into the subarachnoid space If it occurs periodically such oozing may give rise to a syndrome of meningeal irritation resembling that of pachymeningitis hemorrhagica. Rupture usually follows trauma exercise coitus fear or any other condition which elevates blood pressure The evidence of intrameningeal bleeding is obtained by lumbar puncture The spinal fluid is bloody or yellowish in color on account of the presence of derivatives of blood pigment Its cell content may be increased The bloody fluid does not coagulate spontaneously and after sedimentation in the test tube the supernatant liquid remains discolored This is not the case in instances of contamination of the spinal fluid by blood extravasated at the site of the lumbar puncture. Here only the first fluid obtained is bloody there is rapid co

agulation of the admixed blood which settles at the bottom of the test tube and leaves the supernatant fluid clear and colorless Such spinal phenomena as rigidity of the neck and positive Kernig sign are usually present

The symptoms of aneurysm are local and general. An important *general symptom* is *headache* which is often pulsating or migrainous in character It may be associated with vertigo and vomiting *Papilledema* is as a rule absent. Rupture of the aneurysm directly into the sheath of the optic nerve may cause *changes in the fundus of the eye* The hemorrhage may also spread from the subarachnoid space into the optic sheath and appear under the retina

There may be a *murmur* synchronous with the pulse, over the entire skull or over a circumscribed area this murmur however is not pathognomonic of aneurysm as it can be evoked by pressure of a growth on a blood vessel and may also be audible over a highly vascular neoplasm In children it has no significance because it accompanies rickets and hydrocephalus Such murmurs can also be heard in women with vasomotor disturbances and in adults suffering from idiopathic hydrocephalus They are also said to occur in Basedow s disease Compression of the carotid usually abolishes them

Although the symptoms depend on the site of the aneurysm they usually suggest the presence of a lesion at the base of the brain The symptoms progress as the aneurysm increases in size At times apoplectic attacks occur

Aneurysm of the internal carotid usually affects the nerves innervating the eye muscles the olfactory nerve the ophthalmic division of the fifth and the optic nerve It may give rise to exophthalmos amblyopia and various forms of hemianopsia. There may be changes in the disks paralysis of the oculomotor nerve pain hyperesthesia or hypesthesia in the region innervated by the sensory fifth and at times neuroparalytic keratitis Pressure on the cavernous sinus may lead to hyperemia of the retinal veins and dilatation of the superficial veins of the face In cases of left sided lesion pressure on the temporal lobe and peduncle may evoke aphasia and motor disturbances Perforation of the aneurysm into the cavernous sinus causes pulsating exophthalmos The aneurysm may also erode the sella turcica (Bramwell)

An aneurysm of the anterior cerebral artery may compress the optic and olfactory nerves In the middle cerebral artery, it may involve the olfactory nerve in addition to the oculomotor The pressure is for the most part exerted on the brain substance and gives rise to aphasia monoplegia or hemiplegia Aneurysm of the posterior communicating artery may produce hemianopsia by implication of the optic tract

Aneurysm of the basilar artery exerts pressure chiefly against the pons medulla, or peduncle The patient with such a lesion usually experiences pain in the occipital region and difficulty in moving the head. Compression of the pons with symptoms of alternating subacute hemiplegia or bulbar paralysis may be evident Manifestations of irritation or paralysis are sometimes referable to the individual cranial nerves (fifth to twelfth) In aneurysm of the basilar artery the hemiplegia shifts from one side to the other without ever disappearing completely until finally the condition becomes a diplegia or paraplegia Vomiting and respiratory embarrassment are particularly apt to occur in these cases

Aneurysm of the vertebral artery evokes similar symptoms and in some individuals the palate and vocal cord on one side and the hypoglossus on the other side may be involved The author has observed a case of aneurysm of the vertebral artery which gave rise to the syndrome of tumor of the upper cervical cord Cardiac arrhythmia may also be associated with the condition In aneurysm of the posterior fossa forward flexion of the head may evoke respiratory disturbances

The *symptoms* according to Symonds may be classed as local or pressure signs dependent on the localization of the aneurysm those due to the underlying disease and those peculiar to the aneurysm itself *Local* or *pressure signs* include such phenomena as have been enumerated above The symptoms referable to the *underlying disease* are either those of atherosclerosis or infectious endocarditis Disturbances attributable to the aneurysm itself include leakage from the sac meningeal irritation

and the presence of blood in the spinal fluid

The symptoms become acute when the sac ruptures Loss of consciousness is sometimes only slight Blood may escape into the spinal subarachnoid space The appearance of pain and rigidity of the neck after an apoplectic attack suggests subarachnoid rather than cerebral hemorrhage

Diagnosis—The history of a number of attacks of meningeal irritation is suggestive of intracranial aneurysm, especially if the spinal fluid is bloody or xanthochromic In some patients, the syndrome of Weber is produced by an aneurysm near the crus (homolateral lesion of the third nerve and contralateral involvement of the limbs) The fever has been ascribed to effusion into a serous cavity The conjunction of signs of basal meningeal hemorrhage with signs of tumor at the base is evidence in favor of aneurysm especially if these occur during the course of arteriosclerosis or infectious endocarditis (Symonds)

The diagnosis of aneurysm of the cerebral blood vessels is extremely difficult and can usually be made only after death Many experienced clinicians however have ventured the diagnosis on the basis of the clinical syndrome already described Sudden development of coma with hemiplegic phenomena in young individuals without a history of syphilis or hypertension should arouse suspicion The possibility of brain abscess must also be considered in these cases One third of the patients show evidence of intra cranial disease

The condition must be differentiated from *hemorrhagic pachymeningitis* from the various types of *ophthalmoplegia* from *migraine* with or without ophthalmoplegia from *tumor of the trigeminal nerve* and from infectious meningitis If coma is pronounced the disease must be distinguished from *cerebral hemorrhage* Symptoms pointing to the region of the internal carotid (oculomotor signs or trigeminal phenomena) are highly suggestive If in addition we find subretinal hemorrhages bloody or xanthochromic fluid the diagnosis is fairly certain (Symonds)

Owing to the presence of meningeal signs coma fever and leukocytosis the diagnosis of infectious meningitis is erroneously made in some cases of subarachnoid hemorrhage Lumbar puncture promptly clears up the difficulty in diagnosis

Prognosis—The ultimate prognosis in most cases is poor Rupture of the aneurysmal sac with subarachnoid hemorrhage constitutes the chief danger In case of seeping through a very small perforation there may be recovery and the patient may survive for months or even years The prognosis depends somewhat on the primary cause In individuals with extensive atherosclerosis or subacute endocarditis the outlook is poor Death may rapidly follow cerebral compression

Treatment—Lumbar puncture may be employed to drain off the extravasated blood but should not be made a universal practice because the lowering of the spinal pressure entails the danger of reopening the point of perforation and reinducing hemorrhage It may also cause sudden death by jamming the brain stem into the foramen magnum as it does in tumors of the posterior fossa If the signs of cerebral compression are so severe that there is danger to life either lumbar puncture or cisterna puncture should nevertheless be employed. Later on after the acute stage has passed and there are symptoms of meningeal irritation lumbar puncture may relieve the pain

Sinus Thrombosis—*Incidence*—Sinus thrombosis is rarely a primary affection it is usually secondary to phlebitis of the sinus or the veins communicating with it This in turn is almost always the result of an *infectious process in the vicinity of the sinus*

Sinus thrombosis may however be non infectious in origin when it occurs as a sequel of extreme cardiac weakness or of marasmus This type appears in either the very young or the very old In very young individuals it may follow in the wake of exhaustive diarrhea or of long standing suppuration The associated cardiac weakness retards the circulation sufficiently to permit coagulation of the blood In the terminal stage of exhausting diseases like tuberculosis carcinoma persistent typhoid fever and chlorosis the contributory factors are cardiac weakness fatty degeneration of the endothelial lining of the sinus and an increase in the number of blood platelets

Secondary sinus thrombosis usually fol

lows infective lesions adjacent to the sinus or its formative veins it is particularly common in cases of otitis with caries of the petrous bone or the formation of cholesteatoma It is most apt to develop in acute cases of ear disease but may come on at any time. In instances of bone necrosis there may be extensive involvement of the sinus wall or the phlebitis may extend along veins which connect the internal ear with the sinus. It is also frequently complicated by meningitis extradural suppuration or brain abscess Since the thrombosis is usually septic in character the process extends to the jugular vein and leads to general sepsis Sinus thrombosis may also be secondary to necrosis in other parts of the skull It may follow septic affections of the cranium scalp orbit nose or accessory sinuses In infected wounds of the face in facial furunculosis in septic processes involving the neck or the parotid gland and in facial erysipelas the cavernous sinus may become involved owing to extension of the infectious process along the emissary veins

Morbid Anatomy—Sinus thrombosis may be sharply localized or very extensive In the involved sinus either a fresh grayish red clot or an older paler somewhat organized thrombus adherent to the wall of the sinus may be found The older the thrombus the more firm the adhesion In secondary thrombosis the process is often purulent and the wall of the sinus is greenish or greenish yellow in color The purulent material may extend into the jugular and subclavian veins and even into the superior vena cava Streptococci and pneumococci have been recovered from such thrombi There may be destruction of the wall of the sinus with the formation of a perisinuous abscess The unthrombosed part of the sinus is usually very tortuous dilated and distended with blood The parts of the brain from which the involved veins normally carry the blood are hyperemic and are often the sites of capillary or larger hemorrhages

In most otitic cases the lateral sinus is involved while the superior longitudinal sinus is the most common site of marantic thrombosis The cavernous sinus is also frequently affected The involvement may extend from one sinus to another

Symptoms—The symptoms of sinus thrombosis are not characteristic In the marantic type they are obscured by the fundamental condition in the secondary types by such complications as meningitis and abscess Signs of venous stasis may appear *e g* in thrombosis of the cavernous sinus we may find dilatation of the frontal veins cyanosis of the orbital region swelling of the eyelids chemosis and exophthalmos Some observers have noted dilatation of the retrobulbar veins and at times papilledema owing to stasis in the retinal veins. There may be amblyopia Occasionally a history of neuralgic pains in the region innervated by the ophthalmic division of the fifth nerve can be obtained Paralysis of the eye muscles is common

Thrombosis of the sigmoid or lateral sinus leads to edema of the soft parts in the mastoid region and swelling of the upper part of the jugular vein (Jansen found the jugular vein involved in one third of his cases of otitic thrombosis) Sometimes a thickened cord may be palpated. The soft parts may become edematous owing to the presence of lymphangitis near the involved vein the lateral movements of the head become limited and there may even be spasmodic torticollis At times paralysis of the ninth tenth eleventh and twelfth cranial nerves has been observed If either the jugular vein or the lateral sinus on one side be thrombosed pressure on the jugular vein of the sound side may evoke engorgement of the retinal veins * Uhthoff found ophthalmoscopic changes in about 40 per cent of his cases of otogenic thrombosis

Thrombosis of the superior longitudinal sinus leads to dilatation of the veins of the frontal parietal and temporal regions In some cases there may be epistaxis The fontanels may bulge If marantic thrombosis occurs in the superior longitudinal sinus of a child there may be convulsions epistaxis and visible distention of the nasal veins also ensue owing to the communication between this sinus and the nasal veins In cases of primary sinus thrombosis following

* The Queckenstedt maneuver has recently been employed in order to determine the patency of the sinus In cases of complete occlusion of the sinus by thrombosis compression of the jugular vein on the ipsolateral side will not evoke rise in the spinal fluid pressure as determined by the spinal manometer

chlorosis, prolonged diarrhea, or tuberculosis the onset may be acute with violent headache vomiting and stupor There may be convulsions or paralysis, and occasionally rigidity of the neck. The pulse is not typical The patient usually fails rapidly and succumbs within a few days The diagnosis of such a condition depends largely on the knowledge and consideration of the etiologic factors and the slight signs of venous stasis The general symptoms usually arouse suspicion of meningitis or focal disease of the brain (hemorrhage or softening)

The symptoms of secondary otogenic thrombosis vary When thrombosis of the lateral sinus occurs during the course of chronic otitis (without sepsis or complete blocking of the vein) there are fever and headache but these symptoms also occur in meningitis, brain abscess or extradural suppuration

Very often an extradural abscess is the etiologic factor Among the symptoms of extradural suppuration are edema over the mastoid pain on pressure over this area limitation of movement of the head and nystagmus There may also be optic neuritis or papilledema The latter however is more frequent in sinus thrombosis than in extradural abscess

Sinus thrombosis usually gives rise to headache, vertigo, vomiting slowing of the pulse some rigidity of the neck, and other manifestations of meningeal irritation In the septic types such evidences of generalized infection as rapidity and irregularity of the pulse chills fever sweats enlargement of the spleen diarrhea jaundice and metastatic deposits in the lungs and the joints are soon added to the syndrome The blood culture is usually positive

Lumbar puncture often helps to determine whether there is suppurative meningitis in addition to the thrombosis The cerebrospinal fluid is as a rule not under increased pressure it may be sterile (meningitis sympathica) or it may contain organisms In the former case the predominating cells are usually lymphocytes in the latter polynuclears Its sugar content falls rapidly in infectious cases The thrombosis may extend from the lateral sinus to the inferior petrosal and cavernous sinus The latter may be involved on one or both sides

Occasionally evidences of the so-called 'Gradenigo syndrome' appears, this consists of palsy of the external rectus and symptoms referable to the sensory fifth. These are ascribed to an inflammatory process near the apex of the petrous portion of the temporal bone (petrositis) Usually the sixth nerve palsy is transitory

Prognosis —The prognosis of sinus thrombosis is unfavorable although benign types have been described in which the thrombus is absorbed or recanalized This is more apt to occur in primary thrombosis but recovery from the secondary type has also been reported In infectious cases the chief dangers are general sepsis and suppurative meningitis Pyemia seems to develop more readily in thrombosis of the lateral and inferior petrosal sinus than in thrombosis of the superior petrosal and cavernous sinus When the thrombosis extends from one lateral sinus to the other, meningitis is particularly apt to ensue

In modern times the outlook has been improved considerably by early operation A well developed, diffuse meningitis always makes the prognosis poor The incidence of localized meningitis or brain abscess is of serious but less grave significance

Treatment —In primary thrombosis treatment is symptomatic and designed to relieve the underlying condition Stimulats are given the strength of the heart maintained, and nutrition supplied The headache is relieved by an ice-cap or a sedative The patient should remain in bed with the head elevated In infectious thrombosis exploration with free drainage is necessary The treatment should also be prophylactic, including careful treatment of the primary disease (infectious lesions of the face, parotid mastoid) and the evacuation of extradural abscesses Operative therapy has proved very effective and may be employed in cases of septic thrombosis with gangrene of the wall of the sinus repeated chills optic neuritis and profound constitutional symptoms Ligation of the jugular vein has helped in some instances The presence of a diffuse suppurative meningitis is a contraindication to the active treatment of sinus thrombosis but the demonstration of pus cells or bacteria in the spinal fluid does not preclude operation

The recent addition of the sulfonamides to our therapeutic armamentarium will probably help to diminish the incidence of complications of otitis, including sinus thrombosis

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INTRACRANIAL TUMORS

All expanding lesions within the skull may for clinical purposes be regarded as tumors It is only rarely possible to diagnose accurately before operation the exact nature of the lesion on the other hand it is often easy to name its situation in regard to brain areas

These conditions are much more common than has been believed Cushing found in a General Hospital Surgical Service 200 brain tumors in 2500 admissions it is certain that these lesions are often diagnosed as meningitis apoplexy and so on Even in the autopsy room centrally situated brain tumors may often be overlooked if very careful search is not made

Tubercle in mass formation often attacks the pons cerebellum and midbrain of young persons but unless there is calcification of such granulomatous formation capable of obstructing the passage of x ray it is difficult to be sure that such a lesion is not gliomatous in character Gummata of the brain and meninges do not appear in the autopsy room so often as in the textbooks, nevertheless careful exploration for lues must be made in all cases of suspected brain tumor

The frequency of various types of tumors can best be realized from a study of Harvey Cushing s statistics of 2023 cases

	Per cent
Gliomas	42 6
Pituitary adenomas	17.8
Meningiomas	13 4
Neurinomas	8 7
Congenital tumors	5 6
Metastatic and invasive tumors	4.2
Granulomatous tumors	2.2
Blood vessel tumors	2 0
Sarcomas (primary)	0 7
Papillomas (choroid plexus)	0 6
Miscellaneous and unclassified	2.2
	100 0

Various cellular types of tumor show a selective affinity for certain definite regions of the brain for example

Meningioma—Usually in the rolandic zone the sphenoidal wing or the olfactory region
Medulloblastoma—Midline vermis cerebellar syndromes
Astrocytoma—In the cerebellar lobes
Glioblastoma—Most frequently invades the temporal or the occipital lobes
Neurinoma—Most frequently involves the cerebellopontine angle

The commonest types of tumor are glioma and neuroglioma these are rarely discrete and are consequently essentially malignant in behavior Some are highly vascular and into their substance hemorrhages may occur others may undergo cystic degeneration The whorl celled endotheliomata and the fibromata which grow from the acoustic sheath are benign in character Both are encapsulated and grow very slowly they are often meningeal in position and so accessible to operation The slow growth of the endothelial tumor may produce by irritation of the periosteum of the skull such localized thickening of the bone as to invite the diagnosis of primary osteomata

Sarcomata are difficult to distinguish by the naked eye from gliomata they are often

metastatic, as from a hypernephroma, and occasionally pigmented as from the uveal tract Metastases to the brain may occur in both sarcomata and carcinomata, they are usually multiple Primary sarcoma of the base of the skull is not rare in young persons It damages, seriatim the contiguous cranial nerves and is quite inoperable

Symptoms—The symptoms are those due to rise of *general* intracranial pressure headache vomiting and papilledema This triad in the absence of cardiorenal disease is presumptive evidence of an expanding intracranial lesion One or all may be absent Irritative or paretic phenomena of gradually cumulative character may be so precise that the observer can be sure of the presence of tumor formation before intracranial tension is raised sufficiently to give rise to these general signs Papilledema or choked disk is a mechanical process whereby cerebrospinal fluid is forced from the general pond into the potential space of the vaginal sheath of the optic nerves it then appears as a swelling at the nerve head and as it does not involve the nerve fibers directly, it is compatible for weeks or months with normal vision Eventually the albuminous fluid becomes organized the nerve fibers are constricted and consecutive or secondary optic atrophy occurs Sudden blindness may come in cases of severe ventricular distention through bulging downward of the floor of the third ventricle which compresses directly the optic chiasma or the optic tracts behind and to the sides In Bellevue Hospital the release of third ventricle pressure by puncture of the corpus callosum or better still by ventriculostomy (opening the third ventricle wall—Scarff) has relieved this type of blindness Headache is due to stretching of the dura mater, and vomiting to irritation of the center in the medulla which is pressed into the bony ring of the foramen The slow vagal pulse is produced in the same manner Attacks of dizziness are common due to irritation of the labyrinths or other parts of the cerebellar mechanism or they may accompany attacks of transient diplopia Drowsiness frequent yawning and a depression of mental acuity are seen in individuals with ventricular distentions generalized convulsions may occur even though the neoplasm be not placed in either motor area

Focal Signs—In some cases of brain tumor, focal signs and symptoms never appear in others, they are equivocal

Tumors of the Motor Area—These are usually easy of recognition The early appearance of focal epilepsy is presumptive evidence of a lesion affecting either the meninges or cortex A constant site of inception and direction of spread may give precise information as to its position Transient hemiplegia following a focal fit may gradually become a permanent condition If the growth be entirely prerolandic there is no objective sensory loss in the contralateral limbs Should the neoplasm be placed more posteriorly there may be much paresthesia and loss of the sense of position in even the large joints of the opposite side in which case astereognosis would be evident in the affected hand Loss of tactile sense in such conditions is rare and changes in pain and temperature appreciation are unknown

The progress of all tumors one must remember is apt to be slow Deterioration necessarily precedes destruction of function inability to finger a violin properly exists before any appreciable loss of power is discovered. It will be found that lesions of the motor zones if situated on that side of the brain on which the speech faculties are represented produce defects of speech emission comparable to the losses of fine movement just referred to Words come sluggishly and are slurred Inapposite terms are unlikely to occur but accurate descriptions are pronounced badly and with difficulty, hesitation and effort If the growth be low enough to press on the first left temporal gyrus inaccuracies of name and description appear rather than difficulty of emission and articulation

Subcortical growths of the motor areas either do not produce focal epileptic seizures or do so later in the course of the disease Instead a progressive hemiplegia occurs if the tumor be deep enough to infringe on the optic thalamus there may be some alteration of all forms of sensory stimulation on the opposite side of the body which may also be the seat of deep burning pain produced especially by contact with cold or sharp objects. Athetosis is occasionally present

Tumors of the frontal lobes are apt to

give rise to an inapt purposeless jocosity, occasionally frequent yawning and urinary incontinence appear early If the tumor begins in the subfrontal area it may cause pressure on the optic nerve of one side thereby producing a primary optic atrophy without papilledema though the disk on the opposite side is choked Vision there is still normal

Expanding lesions of the occipital lobes are characterized especially by homonymous hemianopic defect in the contralateral visual field Primarily subcortical growths interfere with optic radiations and produce hemianopia primarily cortical lesions of the occipital pole especially of the walls and floor of the calcarine fissure cause visual fits in the opposite visual field followed later by loss of function in that field

These fits consist of crude phenomena lacking constructive quality twinkling or flashing lights in the affected visual field one patient said he saw objects in that field "as though through multicolored rain Alexia or hemianopia may follow visual fits as a transient phenomenon which may later become permanent

Tumors of the temporal lobe are difficult to recognize especially on the right side, owing to the comparative latency of the region affected Irritation of the uncinate lobules however, gives rise to paroxysmal crude subjective sensations of taste and smell and pressure on the neighboring internal capsule may produce a slight hemiplegia of the opposite side of the body pressure on the optic radiations will possibly result in partial quadrantic homonymous hemianopia Further there occur as a result of disturbance of these areas so called temporosphenoidal fits which may consist of true dreamy states in which consciousness though retained is oddly transformed and the relationship between the individual and the external world becomes subjectively altered Some of these attacks are accompanied by remarkable highly constructed hallucinations such as a woman dressed in blue who beckons to me an old woman in stinking rags ringing a bell figures dressed in eighteenth century costumes a lot of Negroes If the growth be on the side of the speech centers there is difficulty in naming seen objects but no real trouble in speech emission This condition is perhaps the most characteristic of all the temporo sphenoidal defects and is dependent on a degradation of function in the association tracts uniting the visual and auditory centers These naming errors are instantly perceived by the patient and annoy him The right word is recognized as soon as it is heard and so far are these people from being word deaf that an inaccurate prompting is always rejected

Tumors of the Centrum Ovale and Basal Ganglia—If the optic thalamus be implicated the syndrome peculiar to disease of this organ appears contralateral athetosis astereognosis and depression of the power to appreciate touch on the affected side explosive sensibility for superficial and deep pain and temperature with subjective burning pain of characteristic nature in the same parts Motor hemiplegia may be slight. Tumors of one striate body do not usually give rise to postural defects such as occur commonly from epidemic encephalitis

Tumors of the corpus callosum are characterized by a slow paralysis of all four limbs Cranial nerve palsies are uncommon The profound interference with association tracts produces blurring of the mind and interference with speech Reflexes may not be abnormal the muscles are waxy and overtoned so that alternating movements are initiated with difficulty One patient under the writer s observation a police sergeant, first discovered his illness by finding himself unable to relax his grasp of an offender s arm'—an instance of forced grasping'

Tumors of the quadrigeminal plate almost always originate in the pineal body in young persons Precocious puberty paints a picture in colors complementary to those used to portray the effects of certain pituitary growths The cerebral tissue is compressed but rarely invaded by glandular hypertrophy the passage from the third to the fourth ventricle may be completely corked by neoplasm and pressure on the oculomotor nuclei gives rise to palsies of conjugate deviation of the eyes upward and downward movements being first impaired Slowness of pupil reaction precedes immobility Nystagmus is almost always present. The gait is ataxic as are also the movements of the arms Bilateral pyramidal tract

metastatic, as from a hypernephroma and occasionally pigmented as from the uveal tract Metastases to the brain may occur in both sarcomata and carcinomata they are usually multiple. Primary sarcoma of the base of the skull is not rare in young persons It damages seriatim the contiguous cranial nerves and is quite inoperable

Symptoms—The symptoms are those due to rise of *general* intracranial pressure headache vomiting and papilledema This triad in the absence of cardiorenal disease is presumptive evidence of an expanding intracranial lesion One or all may be absent Irritative or paretic phenomena of gradually cumulative character may be so precise that the observer can be sure of the presence of tumor formation before intracranial tension is raised sufficiently to give rise to these general signs Papilledema or choked disk is a mechanical process whereby cerebrospinal fluid is forced from the general pond into the potential space of the vaginal sheath of the optic nerves it then appears as a swelling at the nerve head and as it does not involve the nerve fibers directly, it is compatible for weeks or months with normal vision Eventually the albuminous fluid becomes organized the nerve fibers are constricted and consecutive or secondary optic atrophy occurs Sudden blindness may come in cases of severe ventricular distention through bulging downward of the floor of the third ventricle which compresses directly the optic chiasma or the optic tracts behind and to the sides In Bellevue Hospital the release of third ventricle pressure by puncture of the corpus callosum or better still by ventriculostomy (opening the third ventricle wall—Scarff) has relieved this type of blindness Headache is due to stretching of the dura mater and vomiting to irritation of the center in the medulla which is pressed into the bony ring of the foramen The slow vagal pulse is produced in the same manner Attacks of dizziness are common due to irritation of the labyrinths or other parts of the cerebellar mechanism or they may accompany attacks of transient diplopia Drowsiness frequent yawning and a depression of mental acuity are seen in individuals with ventricular distentions generalized convulsions may occur even though the neoplasm be not placed in either motor area

Focal Signs—In some cases of brain tumor focal signs and symptoms never appear, in others they are equivocal

Tumors of the Motor Area—These are usually easy of recognition The early appearance of focal epilepsy is presumptive evidence of a lesion affecting either the meninges or cortex A constant site of inception and direction of spread may give precise information as to its position Transient hemiplegia following a focal fit may gradually become a permanent condition If the growth be entirely prerolandic there is no objective sensory loss in the contralateral limbs Should the neoplasm be placed more posteriorly, there may be much paresthesia and loss of the sense of position in even the large joints of the opposite side in which case astereognosis would be evident in the affected hand Loss of tactile sense in such conditions is rare and changes in pain and temperature appreciation are unknown

The progress of all tumors one must remember is apt to be slow Deterioration necessarily precedes destruction of function inability to finger a violin properly exists before any appreciable loss of power is discovered It will be found that lesions of the motor zones if situated on that side of the brain on which the speech faculties are represented produce defects of speech emission comparable to the losses of fine movement just referred to Words come sluggishly and are slurred Inapposite terms are unlikely to occur but accurate descriptions are pronounced badly and with difficulty hesitation and effort If the growth be low enough to press on the first left temporal gyrus inaccuracies of name and description appear rather than difficulty of emission and articulation

Subcortical growths of the motor areas either do not produce focal epileptic seizures or do so later in the course of the disease Instead a progressive hemiplegia occurs if the tumor be deep enough to infringe on the optic thalamus there may be some alteration of all forms of sensory stimulation on the opposite side of the body which may also be the seat of deep burning pain produced especially by contact with cold or sharp objects Athetosis is occasionally present

Tumors of the frontal lobes are apt to

the vertebrae as in lumbar puncture When intracranial pressure is obviously raised, the former procedure (ventriculography) is safer than the latter (encephalography) Such air *injections should only be done in carefully* selected cases, there is danger of sudden death during the procedure, especially in cases of tumors below the tentorium or of the midbrain Radiotherapy, as yet, has not justified the hopes once placed in it surgery is still the better instrument He who cares *for patients suffering from brain tumor must* bring to his task much thought and stout action There is need, too of formidable optimism for the dice of the gods are loaded!

FOSTER KENNEDY

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ENCEPHALITIS

(Exclusive of Epidemic Encephalitis)

Nervous symptoms of any kind developing during the course of infectious diseases should always bring to mind the possibility of inflammatory changes in the cerebrum, cerebellum spinal cord or the meninges Furthermore it is impossible to speak of encephalitis without recognizing the possible occurrence of a myelitis and so the term encephalomyelitis represents the more accurate conception The meninges are implicated to varying degrees in different cases and yet again a peripheral neuritis may seem to dominate the picture

The inflammatory lesions are rarely if ever generalized in their full intensity but tend to be isolated or patchy in their distribution and many diverse pictures may be presented by different cases suffering from the same types of disease

Attempts have been made to associate certain nervous patterns with the different *underlying infectious diseases*, but although meningeal involvement may usually seem most intense with mumps cerebellar symptoms more often in chicken pox measles and German measles and perhaps myelitis complicating influenza such coincidences are by no means invariable and the obvious *nature of the primary disease usually* renders such speculations useless for clinical purposes.

Etiology—It would seem that influenza is by far the commonest disease to incite encephalitis or myelitis *In addition to this* others acting as incitants are measles *German measles* chicken pox *mumps* whooping cough small pox and psittacosis also occasionally in apparent epidemics vaccinia These it will be noted are all virus diseases, and suggestions have been made that the *complicating encephalitis is due to their re*spective viruses, but the occurrence of encephalitis in the course of certain diseases not of virus nature would seem to invalidate this theory Such diseases are chorea scarlet fever diphtheria tonsillitis putrid bronchitis pneumonia erysipelas typhoid fever, dysentery, typhus fever relapsing fever puerperal and other septicemias Bacterial endocarditis may be complicated by what appears to be a diffuse encephalitis rather than the more discrete lesions due to em*bolism Stuporous states occurring during* epidemics of acute poliomyelitis might legitimately be regarded as a cerebral form of that disease especially where some such paralytic phenomenon as ptosis constitutes a residual It is not always easy to differentiate between a simple delirium occurring in a fever and an encephalitis particularly in senile patients suffering from chronic bronchial infections but postmortem findings may in some instances establish the occurrence of the latter Certainly in none of these latter diseases is it thought that the complicating encephalitis is necessarily due to the organism causing the original disease The suggestion is that a latent virus already within the nervous system is activated or that the primary disease permits the entry of a virus from without.

pressure is usual and produces the characteristic paralysis and alteration of reflexes Severe ventricular distention is the rule

Tegmental growths usually produce a coarse tremor in the contralateral hand through implication of the rubrospinal tract and the red nucleus An ipsolateral third nerve paralysis may occur also Such tumors are often conglomerate tubercles most often found in children and adolescents

Tumors of the pons produce combinations of ipsolateral palsies of the fifth sixth, and seventh nerves together with paralyses of the opposite limbs It is important to determine the nuclear origin of these palsies as abducent lesions often arise from increased general intracranial pressure In such cases however they are not accompanied by ipsolateral facial paralysis nor is the movement of the contralateral internal rectus muscle decreased in amplitude or force Pontine gliosis may be diffuse and produce the appearance of simple pontine hypertrophy Papilledema appears late The fillet is extraordinarily resistant to compression and objective sensory change from this cause is consequently rare

Tumors of the cerebellum may arise within the brain itself or from the infratentorial meninges or nerve sheaths Intracerebellar tumors are soft rapidly expanding and usually malignant while those originating outside the cerebellum are usually hard fibrous and of tardy growth Papilledema appears early Dizziness is common

The sidedness of the growth can usually be determined by the nystagmus motor ataxia decreased muscular tone and weakness Nystagmus is usually slower and of greater amplitude on looking toward the side of the lesion and finer and more rapid on looking away from the lesion The other signs are all more evident on the same side as the tumor Decomposition of rhythmic movement may be present in the ipsolateral arm the finger nose test may be poorly performed on the same side and hypermetria, may also be seen The patient stands less well on the ipsolateral than on the contralateral leg A curious tilted attitude of the head seen in these cases is probably of vestibular rather than purely cerebellar origin

Tumors growing in the *cerebellopontine angle* more often arise from the sheath of the acoustic nerve their first symptom is apt to be tinnitus and vertigo followed by progressive nerve deafness The fifth nerve is next involved, subjective numbness and tingling in the face and the side of the tongue ensues By the time the facial nerve is implicated definite evidence of cerebellar compression is forthcoming These tumors grow slowly, two to five years may pass before successive involvement of contiguous structures makes plain the diagnosis

Tumors of the medulla oblongata produce bilateral pyramidal signs and affections of the lowest cranial nerves which result in difficulties in articulation and swallowing and arrhythmia of the heart and respiration If the fourth ventricle be invaded glycosuria is usual and vertigo becomes even more evident

Tumors of the hypophysis may be recognized both by neighborhood signs and the evidences of altered pituitary function The former is most characteristically bitemporal hemianopia but almost any form of hemianopic defect may occur Choked disk is rare and is seen only when the growth has blocked drainage by invading the fluid ventricle Primary optic atrophy is usual An incomplete Frohlich syndrome—adiposity eunuchism and abnormal sugar tolerance—may be an expression of defective pituitary secretion acromegalic symptoms are less usual

Intraventricular tumors and cysts arise from the choroid plexuses the ependyma or the medullary vela The symptoms produced by these tumors are essentially due to pressure on or invasion of structures bordering on their ventricular position

Treatment —There is nothing to be said for the expectant treatment of brain tumors though headache may be relieved by intravenous glucose solution of hypertonic strength *Action*—even though it be but a decompression operation—should follow diagnosis

A distinction can often be made between similarly appearing cases of expanding and degenerative brain disease by x ray photography of the ventricles and subarachnoid spaces air having been introduced to replace cerebrospinal fluid either through a trephine opening over the posterior ventricular horn or through a hollow needle inserted between

rest In considering the apparent lack of proportion between the severity of the primary disease and the incidence of encephalitis it would seem possible that the milder exanthemata since they do not inhibit the activities of the patient may increase the risk of encephalitis Exertion undertaken too early in convalescence would seem undoubtedly to aggravate the complicating encephalitis. Six weeks absolute confinement to bed is strongly recommended

Medicinally 90 to 120 grains of sodium salicylate with twice that amount of bicarbonate of soda daily appears to accelerate the recovery of some stubborn cases It may be given in divided doses every two hours for two days in succession in each week and repeated if improvement is noted Five grains of hexylamine every hour for nine doses a day may benefit some patients In fulminating cases, 50 cc. of 50 per cent glucose may be given intravenously or 100 cc of 15 per cent sodium chloride with the purpose of reducing cerebral edema Cerebral congestion and edema may also be reduced by free saline purgation or by magnesium sulfate glycerin and water enema in the proportions of 1 2 and 3 ounces respectively

Sulfapyridine or sulfadiazine are indicated in such infections as they have been found to influence but probably no effect is exerted by the sulfa drugs on virus infections Sulfathiazole having little if any power of penetration of the meninges should not be used

Withdrawal of 5 cc of cerebrospinal fluid by lumbar puncture daily or more often is of benefit when meningeal symptoms are troublesome Small amounts taken at intervals are probably more beneficial than larger amounts which might lead to undesirable changes in the cerebral circulation

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ABSCESS OF THE BRAIN

Etiology.—The conditions which may lead to brain abscess by direct extension are *trauma* of the head or face *infective conditions* of the ear, eye or nose and its accessory sinuses and infections of the face and scalp such as erysipelas Metastatic abscess may develop from bacterial endocarditis particularly of staphylococcic origin osteomyelitis bronchiectasis abscess or gangrene of the lung pneumonia rarely pulmonary tuberculosis empyema streptothrix infection, actinomycosis carbuncle, influenza and other infectious diseases septic endometritis following abortion puerperal infection amebic dysentery liver abscess pyonephrosis and epidemic cerebrospinal meningitis Metastatic abscesses are likely to be multiple whereas those due to direct extension are usually solitary

Septic diseases of the ear are the most common cause of brain abscess and are responsible for 33 to 50 per cent of the cases seen in civil practice Chronic aural diseases cause many more brain abscesses than acute ones. Otitic disease may extend into the brain along thrombosed blood vessels or lymphatics The infection may travel along the seventh or eighth cranial nerve Granulations which develop after operation may block free outward drainage and force infection into the brain Sequestra in the temporal bone may be the exciting cause Extension from the ear may take place through the roof of the tympanic cavity into the temporal lobe of the cerebrum or from the mastoid cells into the cerebellum. Possibly in a large proportion of cases of aural disease there is some degree of serous, sterile meningitis but something more than this is required to cause abscess Even extradural or intradural collections of pus may not lead to abscess

Trauma of the head, not necessarily fracture of the skull is the next most frequent cause Brain abscesses have apparently resulted from injuries which affect neither the skull nor even the scalp seriously but the condition may be an extension from infected bruises of the scalp One would expect an abscess resulting from a head injury to be located near the surface of the brain but this is not always the case especially if the infection has been carried to

A different and really noninflammatory condition is that caused by malaria in which clumps of plasmodia may plug the smaller vessels of the brain or cord Syphilis, except perhaps in the case of general paresis acts through its destructive action on the blood vessels this leads us to consider some of the exogenous poisons such as arsenic and carbon monoxide as well as trauma which act on the brain only indirectly as the blood ves sels thereof degenerate or are otherwise in jured Caisson disease and fat embolism pro duce nervous symptoms by local anoxia Lead thallium and many other exogenous poisons used in industry particularly the solvents or dopes act more directly on nerve cells causing degeneration and some of them on the white matter of the central nervous system or on the peripheral nerves producing toxic degeneration rather than inflammation

Morbid Anatomy —Vascular congestion and edema most obvious in the gray mat ter and in some instances hemorrhages are found These are accompanied by more or less degeneration of cortical cells Perivas cular demyelination in the white matter characterizes other cases and perivascular cuffing is frequently found in such instances Glial proliferation is possibly a result rather than a part of the acute process Some of the most fulminating cases may show almost no postmortem changes

Symptoms —Special attention should be directed to the milder symptoms such as vertigo and numbness and tingling in vari ous parts of the body The two latter may or may not be accompanied by objective sen sory disturbances and all three in themselves may seem trivial until motor phenomena develop with the risk of serious disability Such are cranial nerve palsies particularly of the eyes hemianopia aphasia mono plegias hemiplegia paraplegia often of the ascending type and with or without sensory loss chorea athetosis incoordination sug gesting cerebellar disturbance and more spectacularly convulsions

It is perhaps more common for these to develop without such symptoms as head ache stupor and neck rigidity in cases of milder onset yet not a few such mild cases progress to serious and permanent dis ability

There would seem to be no correlation be tween the occurrence of encephalitis and the severity of the primary disease in fact it often complicates the milder forms of infec tion for reasons that will be speculated upon under treatment

The *temperature pulse rate* and *respira tory rate* are not much raised in the average cases which however may run a protracted course and leave permanent effects A tem perature rising to 104° F for more than the first day or two carries with it a grave prog nosis The pulse rate may be accelerated by changes in the heart or it may be acceler ated or slowed by disturbances of nervous control Tachypnea has been observed re sulting in a fatal issue A few cases result fatally from paralysis of breathing or swal lowing

The *reflexes* are frequently reduced or abolished in the earlier stages but later may become increased in those cases likely to leave permanent effects in the form of hemiplegia or paraplegia

Laboratory findings are on the whole of little assistance in the average case The white blood count is rarely much raised in the favorable type of case, the cerebrospinal fluid usually shows only a moderate pleocy tosis of less than a hundred cells per cubic millimeter, and some increase of the total protein content Xanthochromia may also occur but all such changes in the spinal fluid probably depend on the approxima tion of the inflammatory changes to the meninges and severe cases may run their courses with little if any change in the cerebrospinal fluid except an increase of its pressure

Prognosis —As regards life the prog nosis is usually most favorable except in the hyperpyrexial cases As to permanent dis abilities they would seem to be dependent on the success of treatment although on the whole they are not greatly to be feared Aphasia and epilepsy have been seen to fol low chorea in a child Spastic paraplegia or some degree of hemiplegia is not uncommon Such residuals are not however as common as the sequelae of epidemic encephalitis (See p 63)

Treatment —Of all forms of treatment the writer would like to emphasize most strongly the beneficial effects of prolonged

rapidly enough or become sufficiently extensive to cause shock but when only the surrounding areas of congestion and edema implicate these motor areas or tracts, spastic disturbances are more likely to ensue Furthermore, if the paralysis of a part be incomplete the abscess is probably not exerting its destructive action at the center representing that part and careful search should be made for signs of more complete loss of other functions This statement, however, must not be too literally accepted in the case of facial paralysis referable to the upper motor neurons since under these circumstances the lower part of the face is affected much more than the upper part and the paralysis even of the lower face is frequently inconstant and incomplete The paralysis may be complete hemiplegia or be restricted to as small an area as the thumb The minute lesions are liable to spread and the more or less rapid involvement of one part after another may be important in differentiating brain abscess from a neoplasm

Convulsions are suggestive of abscesses at or near the cortex purulent conditions within the ventricles have been found to cause great *drowsiness* or *coma*

The *reflexes* both tendon and cutaneous demand careful interpretation. Reduction or actual loss of the tendon reflexes and of the cutaneous reflexes with more or less weakness and hypotonia of the corresponding limbs suggests a homolateral cerebellar lesion but as has been pointed out above might be produced by a contralateral lesion of the upper motor neurons Disturbances of the tendon reflexes may be interpreted as an increase of those of one side above normal (contralateral lesion of the pyramidal tract) or a reduction of those of the other side below normal (ipsolateral cerebellar lesion) In the first instance some degree of spasticity probably exists in the corresponding limbs and the plantar cremasteric abdominal and epigastric reflexes may determine diagnosis In the second instance hypotonia and ataxia out of proportion to the actual muscular weakness may be the deciding factors

Homonymous hemianopsia may be caused by an abscess in the occipital lobe but if accompanied by hemianesthesia the region of the posterior limb of the internal capsule is involved If hemiplegia exists the anterior limb of the capsule is also included

Aphasia in its different forms may help locate the abscess but is often misleading possibly because the popular conception of the speech areas is incorrect but undoubtedly also because pure types of aphasia are rare The speech centers are located in the left cortex in right handed people and sometimes in the right cortex in left handed people *Anomia* is the sign most commonly produced by abscess of the brain because the purulent processes so frequently occur in the temporal lobe following aural disease Incomplete *sensory* or *motor aphasia* may in some cases be confused with the indefinite mental changes and so lose its value as an aid to localization

Astereognosis may aid diagnosis of abscesses of the parietal lobe but care must be taken to distinguish this condition from aphasia which prevents description of things the patient recognizes and can name

Olfactory hallucinations especially if associated with convulsive attacks or *periodic dream states* are indicative of a temporosphenoidal lesion Abscesses of the midbrain pons and medulla are rare and almost certainly fatal *Eye palsies nystagmus facial paralysis difficulty in swallowing respiratory disturbances* (Cheyne Stokes respiration) and various *pulse disturbances* may be expected to occur just before death Implication of the cranial nerves is more often produced by pus in the meninges than by abscess in the brain stem

Diagnosis —Abscess of the brain is often difficult to recognize on account of the frequent absence of signs and symptoms and the possibility of misinterpretation of those which appear

Choked disk may be absent in a greater proportion of these cases than in those of brain tumor possibly because the process is largely one of breaking down tissue rather than of additional growth For the same reason headache may not be a prominent symptom and vomiting may occur no more frequently than in mild gastro intestinal disorders It is frequently accompanied by nausea Intracranial disease may not be suspected by those who place too much reliance on projectile vomiting

some depth by a fragment of bone or a foreign body

An exacerbation of symptoms or the appearance of new symptoms several days after injury of the head should arouse suspicion of abscess of the brain After such injury or in disease of the ear and nose meningitic symptoms may mask those of brain abscess

Morbid Anatomy —An abscess of the brain is a softening which usually contains greenish pus In chronic abscesses this pus may be sterile or contain organisms of all kinds Abscesses which develop during exanthemata often contain organisms not usually associated with the primary disease. The lesion may or may not have a well-formed wall In many instances there is merely a simple gradation from pus to softened brain tissue, edema, and hyperemia while in others a somewhat hardened yellowish wall forms which is perhaps a protection against spread of the disease Some abscesses rupture into the ventricles of the brain Evidence of the spontaneous healing of others is thought to be the calcified nodule occasionally discovered after death

Symptoms —Brain abscesses may be acute or chronic that is the development of the abscess may fairly rapidly produce symptoms which cause death or demand immediate treatment or run a slow insidious or apparently asymptomatic course without evidence of the pathologic process until an exacerbation of symptoms or even autopsy reveals its existence. Such chronic abscesses may persist one or two years or more rarely for ten, twenty, or thirty years Those situated in the depth of the brain tend to remain quiescent longer than those near the surface

The *general symptoms* of both chronic and acute abscess of the brain are general malaise loss of weight poor appetite constipation, furring of the tongue and a heavy breath Chills are not common but may occur The patient may not be aware of fever, and the temperature may never except in the more acute conditions or terminal stages rise above 100° F Jaundice may be noticeable in the more chronic cases When abscesses break into the ventricles general convulsions delirium stupor tetaniform spasm chills, hyperpyrexia rapid pulse and respiratory disturbances result to be followed by death with signs of meningitis within a few hours

In addition to these general symptoms there may be *certain evidences more suggestive of intracranial disease* i e those associated with increased intracranial pressure (headache, vomiting, and papilledema) as well as mental signs suggesting hysteria neurasthenia unaccountable change of character or even a definite psychosis The most helpful indications of all are those physical signs which not only point with certainty to disease of the brain but may even indicate clearly the particular area involved

Of the signs of increased intracranial pressure associated with abscess of the brain *headache* is the most constant Any constant, or frequently recurring headaches especially those which prevent sleep, are most suggestive of intracranial hypertension The location of the headache may vary or, if fixed be remote from the seat of the disease In some cases the skull is tender on percussion. The headache is very often of the congestive type that is intensified by stooping, coughing and straining at stool

The *mental symptoms* of brain abscess are most varied and it is doubtful if the lesion can be localized with any accuracy by their nature Hallucinations of formed images have been considered characteristic of disease of the temporal lobe Delusions, disorders of memory, retardation and other symptoms suggesting either indefinite or well recognized psychoses may occur Difficulty of concentration, susceptibility to mental and physical fatigue moral turpitude, insomnia, restlessness, irritability, drowsiness and an infinite variety of mental disturbances result from such disease but without the physical signs do not indicate the probable location of the lesion

Signs —Physical examination is of the utmost importance since it alone indicates which area of the brain is to be explored Its nature is suggested by the character of some of the more common signs *Paralysis* of a part or a whole side may follow involvement of the motor area or its vicinity and of the pyramidal tract in the corona radiata internal capsule or crus It may be of the flaccid type if the abscess has developed

sage through arachnoid villi into the venous sinuses and partly by less obvious paths

The various lesions producing hydrocephalus do so by interfering with this normal circulation and absorption Leaving out of consideration the pressure of tumors which cannot be considered here the block may be the result of congenital anomaly infection or injury The aqueduct may be blocked by *failure of development* which results in obliteration of its lumen Naturally such a condition causes distention of the ventricles which cannot be drained by lumbar puncture When spina bifida exists hydrocephalus may occur either at birth or after surgical treatment of the spina bifida The exact relation between the two conditions is not clear but there is no question that hydrocephalus is one of the most serious dangers involved in surgical relief of the meningocele of spina bifida

Infections in fetal life or later may obliterate the foramina of Magendie and Luschka and prevent the flow of fluid into the subarachnoid space. This causes hydrocephalus and the fluid cannot be drained by lumbar puncture Any serious adhesions about the midbrain or extensive obliteration of the subarachnoid space over the hemispheres prevents fluid from reaching the areas where greatest absorption takes place The ventricles can be easily drained by lumbar puncture however and to this type the name of communicating hydrocephalus has been given to distinguish it from the obstructive' or noncommunicating types.

Injuries particularly the common birth injuries involving tentorial tears may result in effusion of blood and arachnoid tears about the midbrain Adhesions may form and prevent entrance of the fluid to the absorbing area As Beneke pointed out injury of the vein of Galen may produce back pressure on the choroids Whether this is a common cause of hydrocephalus is doubtful but Dandy and Blackfan s work lends support to the theory

Symptoms —Advanced hydrocephalus in infancy is unmistakable The child s head enlarges with a great disproportion between the normal face and the large cranial vault The sutures spread the fontanels enlarge and become tense and the eyes are dislocated downward by pressure upon the thin orbital plates For a time even in rapidly progressive cases the baby may remain bright maintain its nutrition, and show no evidence of cerebral involvement but sooner or later unless the process is arrested the thin cortex fails to resist the constant pressure and idiocy spasticity and optic atrophy result with eventual death from malnutrition or intercurrent infection In other instances the condition is arrested before serious damage occurs In some of these babies the hydrocephalus is so transient that downward dislocation of the eyes and bulging of the fontanel alone suggest the accumulation of fluid

Obviously the signs are quite different if the increase in fluid takes place after the skull has become rigid Headache vomiting thinning of bone early optic neuritis or atrophy dominate the syndrome These late cases however are usually the consequence of meningitis or of tumor and cannot be discussed in detail here

Diagnosis —The absolute diagnosis of internal hydrocephalus depends on the demonstration of enlarged ventricles If on lumbar puncture hardly any fluid can be obtained it is fair to assume that noncommunicating hydrocephalus exists if on the other hand the fluid flows freely and the fontanel becomes soft it is reasonable to conclude that a communicating type is present There is I believe only one important error that occurs with any frequency If enlargement of a baby s head is due to subdural hematoma surgical relief is urgent The paper of Ingraham and Heyl on this subject demands careful consideration

The diagnosis can be made more certain by puncture of the ventricle through the lateral angle of the anterior fontanel The dilated ventricle can be easily tapped and of course the thickness of the cortex measured by observing the depth at which fluid is obtained Dandy s method of ventriculography after injection of air furnishes absolute evidence of internal hydrocephalus Whether it is a reasonable procedure is a question The therapeutic resources are so few and the added information gained is so slight that the writer doubts its usefulness Certain it is by no means a trivial operation though before the closure of the sutures

The differentiation of brain abscess from *brain tumor* depends on the development of fever and leukocytosis as signs of infection These symptoms may, however be absent in the former condition or be caused by incidental factors during the latter Chills are most suggestive of abscess as are also the rapid development and extension of signs and symptoms but it is to be remembered that *hemorrhage into a glioma* may evoke the *same symptoms* The *absence or late* development of choked disk can be more readily explained by abscess than by tumor

The symptoms produced by some brain abscesses may be simulated by *uncomplicated otitic disease* and by exacerbations of chronic disease of the ears The disappearance of such conditions after operation on the ear or their failure to develop farther if the operation fails to abolish local infection entirely, offers some reassurance although continued observation is necessary *Meniere s disease* occurring in isolated attacks with complete recovery and absence of physical signs between exacerbations should not offer difficulty An *extradural abscess* is not likely to produce localizing signs or those of increased intracranial pressure but may cause tenderness and edema of the scalp far in excess of that produced by abscess of the brain

Diffuse purulent meningitis can be diagnosed with certainty by lumbar puncture If pus be found in the cerebrospinal fluid in the case of brain abscess there is also meningitis and the diagnosis of abscess must depend entirely upon the localizing signs

The sedimentation rate may be of aid in differentiating brain abscess from cerebral neoplasm

The *traumatic and reflex neuroses hysteria neurasthenia* and the *psychoses* may confuse diagnosis at times The presence of recognized physical signs of organic disease of the nervous system should prevent diagnosis of these conditions unless they can be referred to some preexisting changes It is not safe to diagnose these disturbances merely by a process of exclusion and if there is evidence of a possible abscess of the brain such diagnoses should be made only with the greatest reluctance

Prognosis—The prognosis is always serious Most brain abscesses lead to death

Treatment—The only treatment is surgical both with regard to the primary course of infection, particularly mastoiditis or sinusitis, and also in locating and evacuating the abscess This latter may often be done through a small burr hole remote from the infected area preventing later herniation of brain tissue through a large cranial defect then through this canal and the underlying clean brain tissue needling the abscess

Chemotherapy has not proved effective in the treatment of abscesses in themselves but should be employed for its possible effect on the source of the infection

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INTERNAL HYDROCEPHALUS

Definition—Internal hydrocephalus is a condition characterized by an increased accumulation of fluid within the ventricles of the brain

History—Dandy and Blackfan in 1914 published a paper giving pathologic and experimental data which established a definite conception of the condition and rendered previous discussions of purely historic value

Etiology—An elementary knowledge of the physiologic factors governing the formation of the cerebrospinal fluid is essential to the understanding of the pathology of hydrocephalus In details there are many points where evidence is lacking or where opinions clash but it is clear that most of the fluid forms in the choroid plexuses within the ventricles and flows through the aqueduct of Sylvius to the fourth ventricle whence it escapes into the subtentorial subarachnoid space Part goes down into the spinal canal part flows upward through channels about the midbrain and reaches the subarachnoid space over the cortex of the cerebrum It is here that absorption in large measure takes place partly by relatively direct pas

alysis. The importance of birth injury is further emphasized by the fact that it may cause idiocy and epilepsy which are of great social and economic importance

Etiology —In this discussion the fetus during birth can be considered as a central nervous system surrounded by a relatively fragile envelope of flexible bone and connective tissue During the act of birth this envelope yields to force with consequent distortion Obviously the central nervous system is affected by pressure but remains undamaged if the balance between the forces imposed and the resistance of the fetus is not disturbed The fetus perishes if the vital centers of the medulla and the upper cord are seriously damaged but it may survive serious destruction of the cord below the vital level or of the brain above the medulla Usually although not always cord injury is the result of the maneuvers incident to breech extraction or to accidents consequent to severe traction on the brachial plexus.

Symptoms —The character of the symptoms is determined by the extent and location of the injury In a general way it can be assumed that injuries high in the cord will cause death by damage to the phrenic nuclei while subtentorial damage will probably cause death by pressure upon the medulla For practical purposes therefore it is essential to consider the physiologic disturbances due to cord injury below the fatal region or to cerebral damage at the midbrain or above

The intracranial injuries affect two different parts of the brain If the hemorrhage as usually happens is from branches of the vein of Galen or from that vessel itself the chief damage will occur in the subcortical regions notably in the basal ganglia. The consequence will be general disturbance of associated movements involving rigidity and athetosis If the circulatory disturbance is severe enough to involve the internal capsules as they pass between the basal ganglia spasticity will be added to the syndrome

In more severe cases practically complete decerebration may occur and lead to rigidity and idiocy In other cases prolonged labor particularly after the rupture of the amniotic membranes give rise to edema and extravasation of blood which is widely scattered within the substance of the brain Such lesions may easily produce diffuse injury to cortical cells and cause idiocy without conspicuous motor disturbances

Although our understanding of epilepsy is too slight to allow dogmatic assertions as to its etiology it is quite clear that among the infinite varities of damage caused by meningeal or intracerebral injury some may cause attacks

The fundamental point about the symptoms of cerebral injuries is that the symptoms produced by the injury are exactly analogous to those produced experimentally in animals The possible variations are infinite In order to understand them it is essential that the child should be considered from a physiologic point of view It is necessary to get away from a preconceived idea of spastic paralysis and from the still more mischievous notion that cerebral palsy means mental deficiency and to find out by rather simple physiologic reasoning what the undamaged residue is Upon this residue rather than upon what is gone depend rational prognosis and treatment.

Diagnosis —To determine whether any particular neurologic lesion dating from early infancy is due to birth injury faulty development or infection is frequently impossible Certain syndromes however such as mongolian idiocy congenital hydrocephalus microcephalus or spina bifida can be clearly distinguished and likewise the various familial degenerative diseases such as Werdnig Hoffmann progressive atrophy pseudohypertrophic muscular dystrophy Friedreich s ataxia and so on

There remains however a great group of nonprogressive conditions which may be considered from two points of view From the first the physician may attribute to birth injury only those conditions with conclusive history He will then be forced to rely on vague conceptions of heredity fetal infections and faults of development conceptions which although safe from an argumentative standpoint lead nowhere in particular The second point of view depends on the pathologic evidence that the central nervous system of babies dying at birth or shortly thereafter shows evidence of vascular injury in at least 50 per cent and prob

the risks are not great In children with rigid skulls injection of air is a major operation involving serious risks Injection of dyes into the ventricles with later attempts to recover them from the spinal fluid or the urine furnishes a valuable means of studying the conditions present but again adds to the risks without giving definite indications for treatment

Treatment —Drugs and endocrine therapy are illogical and of unproved efficiency The one exception is the indication for mercury and salvarsan in luetic cases If *syphilis* be present particularly with involvement of the cerebrospinal system demonstrable by examination of the spinal fluid active and persistent antiluetic treatment must be instituted As Jeans has pointed out, this treatment should be as vigorous as that used in adult cases

Early in the course particularly after birth injuries or meningitis *drainage* either by lumbar or ventricular puncture may be a life saving temporary measure or may aid reestablishment of normal circulation In these cases puncture should be repeated frequently enough to prevent harmful pressure, until it is clear that the condition is permanent, or until equilibrium between production and absorption is established One danger must be faced If spinal puncture does not drain the ventricles it is obvious that it will do harm because the release of pressure below may favor herniation of the medulla

Prompt release of cerebral pressure by ventricular puncture is necessary under these conditions

Surgery is the only hope in progressive hydrocephalus The problem is largely ethical for although no operation offers great hope, the alternative is so appalling that well considered skilfully performed operations are justified if the parents request them An almost infinite number have been suggested The fundamental objection to most of them is that the success depends on the establishment and maintenance of a path from the ventricles into the subarachnoid space and the tendency of the injured arachnoid to form adhesions has I believe never been overcome Dandy has extirpated the choroid and feels that this serious operation offers hope In Bellevue Hospital remarkable success is said to have followed the operation of ventriculostomy, *i e* opening the wall of the third ventricle. The whole question really comes down however to the search for a logical alternative to disastrous inactivity

BRONSON CROTHERS.

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BIRTH INJURIES OF THE CENTRAL NERVOUS SYSTEM

Under the classification of birth injuries is included any condition which may justly be ascribed to damage to the nervous system of a normal fetus as the result of the forces of labor asphyxia accident or hemorrhagic disease within the first few days of life It should be constantly borne in mind that the occurrence of a birth injury does not necessarily imply that obstetric care has been incompetent or unwise

History —W J Little established in 1861 the relation between difficult labor and disorders of the nervous system At irregular intervals since that time many authors have added important evidence until gradually a clear understanding of the various pathologic lesions and their effect upon the development of the child has been built up It is possible to explain with reasonable accuracy how the forces imposed upon the baby act upon the fetal nervous system

Incidence —It is probable that injury of the central nervous system during birth or immediately thereafter accounts for more than half of the deaths of viable babies Furthermore it is almost certain that such injuries are responsible for the disability of more children suffering from organic diseases of the nervous system than any other single etiologic factor except infantile par

nerves, when it is known as a "multiple neuritis" or "polyneuritis."

Mononeuritis (*Localized Neuritis*).—Although the disease may be limited to a single nerve trunk, as in traumatic neuritis, several nerves may often be involved. The condition is then termed "mononeuritis multiplex."

Etiology.—Localized neuritis may result from trauma, chronic intoxication, infection, extension of inflammation, and chilling. Not only direct *injury* of the nerve but also the contusion, traction, and compression resulting from forced muscular movements, the tearing and stretching caused by dislocation or fracture, the reduction of dislocations, and the traction on the head or arms of the infant during labor may evoke mononeuritis. Other etiologic factors are compression by callus, exostoses, cervical ribs, tumors, hypertrophic osteo-arthritis, and repeated severe compression by crutches or industrial instruments, accidental hypodermic introduction of chemical (arsphenamine, sera, ether, alcohol, etc.). *Chronic intoxication* by alcohol or metallic poisons frequently renders a nerve so sensitive that a subsequent slight injury may produce neuritis. During and after *infectious diseases* (typhoid fever, smallpox, diphtheria, tuberculosis) neuritis may develop in its localized as well as in its multiple form. Focal infection, particularly in the tonsils or teeth, is often the cause of a mononeuritis and sometimes of a polyneuritis. *Extension of inflammation* from adjacent parts (caries, bone syphilis, and more rarely diseases of joints) also causes the disturbance. *Cold* is an etiologic factor which has been overemphasized, although it is a common precursor of peripheral facial palsy.

Morbid Anatomy.—An inflammation of the nerves may originate in and be practically limited to the perineurium (perineuritis), be situated mainly in the interstitial tissue (interstitial neuritis), or within the nerve fibers (parenchymatous neuritis). In the first two conditions the nerve is swollen, infiltrated, and red. An exudation of migrating leukocytes is found in the fibrous framework of the nerve. The nerve fibers may not be involved, but there is usually an increase of the nuclei of the sheath of Schwann. The myelin is fragmented and the axis cylinders at times become varicose or undergo granular degeneration. Finally, the nerve fibers may be completely destroyed and replaced by fibrous connective tissue.

Parenchymatous or degenerative neuritis produces a lesion similar to the wallerian or secondary degeneration which occurs in the peripheral end of a severed nerve. It first affects the medullary sheath, then the axis cylinder, and last the neurilemma. The myelin becomes turbid and splits into fragments, small globules, and granules. The axis cylinder likewise becomes subdivided, swollen, and liquefied. Extravasated leukocytes engulf the disintegrated products and become granule or scavenger cells. The neurilemma and its nuclei frequently remain intact. The nerve shrinks in volume and appears grayish, grayish red, or translucent and may finally appear as a fibrous cord. The inflammation is sometimes limited to a portion of the nerve or to several isolated areas. Occasionally the whole trunk may be affected. Thus a focal, a disseminated, and a diffuse neuritis are described.

Recently clinical and pathologic evidence has been adduced to raise the question of whether in such cases as are characterized by degeneration the term "neuritis" should be used or be replaced by "neuropathy." Thus it has been shown that the pathology in the multiple neuritides associated with beriberi, pellagra, alcohol, lead, and other heavy metallic poisoning is uniformly one of a true degeneration.

Symptoms.—The symptoms may be divided into two groups: loss of function of the nerve and irritative phenomena of the inflammation. The first group when present differ only in degree; the second are variable and inconstant. In conditions due to trauma the loss of function produces flaccid paralysis with atrophy and reaction of degeneration in the affected muscles, sensory loss, and at times trophic disturbances. Unless the median or internal popliteal nerves are affected, pain is not a constant, severe, or prominent symptom. Various paresthesias, crawling, slight burning, and formication may be present. When the median or internal popliteal nerves are affected an exceedingly painful type of neuritis (causalgia) may appear. This is characterized by severe diffuse burning pain which is increased by movement, sudden noise, or other startling occurrences. It is partially relieved

ably in about 65 per cent of all cases Such evidence leads to the conviction that a baby of apparently normal development at birth who presents evidence of neurologic disturbance is handicapped by the results of the forces used in bringing him into the world Such a view is unquestionably difficult to establish, but it presents points of value Prophylaxis may be rendered possible by certain revisions of obstetric technic The horror of tainted heredity or other menacing phrases being eliminated the way is prepared to study the physiologic possibilities of a central nervous system damaged by sudden accident

The essential points in diagnosis are to differentiate the fixed nonprogressive type of disturbance from the progressive type and to bear in mind that tumors occur in babies

Treatment may for convenience be divided into measures for the immediate relief of injury and the later efforts to minimize the existing physiologic disturbances

The recognition of increased intracranial pressure is the most important single point in caring for the injured baby after birth Munro and Eustis advocate early lumbar puncture with manometric observations on the cerebrospinal pressure followed in many cases by repeated drainage if the pressure remains high This relatively simple procedure supplemented by ventricular puncture and by transfusion where there is adequate evidence of decreased coagulation constitutes the immediate therapeutic measures Decompression is a serious operation and on the whole is falling into deserved disrepute Ingraham and various others emphasize the frequency of subdural hematomata and properly urge search for evidence by puncture of the subdural space even if the skull must be trephined

Later on operative intervention to attack the intracranial or intraspinal lesion is extremely unsatisfactory Most surgeons after considerable experience have abandoned such operations or perform them only as desperate measures

The effort of the physician should be centered upon the attempt to make use of every bit of intact nervous tissue and to avoid hopeless therapy Idiocy severe convulsions and disability due to total transection of the spinal cord cannot in all probability be relieved by treatment On the other hand practically every child with less than these maximal disabilities is worth working over

Education, patiently and hopefully carried on restores certain patients to efficiency Orthopedic procedures of infinite variety may help but it cannot be too persistently repeated that the successful education of the child handicapped by birth injury is of primary importance and that this education cannot be properly directed unless a clear survey of the physiologic assets is made at the beginning of treatment In every case educational measures should be reappraised at intervals Optimism may be carried to a harmful extent The services of a skilful psychologist should be called upon to help in judging intellectual capacity in certain cases since in many of these children specific disabilities exist

BRONSON CROTHERS

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DISEASES OF THE PERIPHERAL NERVES

NEURITIS

(Inflammation of the Nerves)

Neuritis is an inflammation of the nerves It may involve a single nerve when the condition is known as a mononeuritis or localized neuritis or a large number of

zation of vitamins in food which may be adequate Thus it may occur in gastro intestinal disturbances resulting from alcoholism primary anemias malignancy, old age and functional intestinal disturbances Furthermore when the intake is adequate and the factors satisfactorily utilized there may be an increased vitamin requirement and unless this is supplied by additional diet or active factors deficiency effects may ensue Among such conditions are overwork prolonged emotional strain, excess of carbohydrate in the diet states of increased metabolism fever infectious processes, pregnancy etc

Morbid Anatomy—It is now generally admitted that multiple neuritis is not confined to the peripheral nerves The nerve lesion is only part of a general intoxication which affects the spinal cord and the brain In one of the types described by Osler acute febrile polyneuritis widespread changes in the posterior root ganglia spinal roots, ventral horn cells and Betz cells of the cortex occur The condition differs from acute infectious multiple neuritis (acute pernicious multiple neuritis Heine Medin disease) which is allied to poliomyelitis occurs during epidemics of this disease and usually proves fatal within a few days or weeks Foster Kennedy has described a type of polyneuritis which he designates as *neuronitis*—in which the entire neuron is affected—the spinal roots, especially in the cauda equina and at times also the cord itself

The alcoholic paralysis undoubtedly due to polyneuritis may be associated with slight central changes in the spinal cord The central changes in diphtheritic paralysis are even more marked Lead sometimes affects the spinal cord and frequently the brain Arsenic more rarely affects the spinal cord So-called diabetic neuritis has been shown by Kraus to be in many cases a disease of the posterior roots and posterior columns of the spinal cord

Symptoms—Whatever the cause the general symptoms of multiple neuritis are similar and vary only because of the characteristics of the particular intoxication or infection The disease often begins with prodromata which sometimes persist for weeks The patient complains of numbness slight fever tingling in the extremities and sensations of heat and cold weakness then follows either suddenly or subacutely At times the paralysis is accompanied by fever Convulsions may occur particularly in children Some pain develops and the weakness increases The muscles and nerves become very tender while the skin may be reddened or slightly edematous. After a few days the patient may be unable to stand Complete paralysis of the anterior tibial muscles and of the extensors of the wrists may ensue after a week or two

The *paralysis* is flaccid and is followed by atrophy and other trophic changes The response to electric stimulation varies from an early loss of reaction to faradism to the complete reaction of degeneration The paralysis *is usually symmetric Certain groups of* muscles (the extensors) are more susceptible than others One of the characteristic features is the association of *sensory changes* with the paralysis Tactile anesthesia often associated with hyperalgesia may be an early symptom Later the temperature and pain senses are diminished and retarded The sensory loss is either patchy or diffuse The frequent loss of deep sensibility produces a pseudotabetic or ataxic form of the disease (diabetes diphtheria)

The *deep reflexes* are usually diminished or absent and the superficial reflexes disappear As a rule the distal portions of the extremities are the first to be affected In rare instances the motor cranial nerves may show the first signs The bladder may occasionally be affected for a short time Other visceral reflexes are not disturbed

Special characteristics of certain forms of multiple neuritis are noteworthy *Alcoholic polyneuritis* most often affects women The extensors are the muscles usually involved this produces foot drop and wrist drop The sensory symptoms are variable The course is as a rule favorable Mental symptoms are striking delirium is common and hallucinatory states delusional states and delirium tremens may occur In other cases Korsakoff s syndrome characterized by disorientation loss of memory for recent events and fabrication appears Jamaica ginger paralysis due to adulteration by tri orthocresyl phosphate produces a degeneration of the myelin sheaths of the peripheral nerves and changes in the anterior horn cells *Arsenic polyneuritis* resembles alcoholic

by continuous application of moist dressings So severe is the pain and so urgent the need for moisture that wounded soldiers under fire have often been known to apply rags saturated in urine to the sensitive areas

The consistency of the symptoms due to injury leads to the conclusion that many manifestations of the conditions due to other causes are the result of pathologic changes outside the nerve In disturbances due to sepsis arthritis and infectious diseases, pain is a prominent symptom It is dull aching boring at times continuous at times throbbing and often complicated by sharp lancinating lightning like flashes Nocturnal exacerbations are common All movements which tend to stretch the affected nerve increase the pain it is also aggravated by coughing sneezing and straining Frequently the pain is increased by distortion of the inflamed parts about the nerve as by an arthritic joint for example. The inflamed nerve may be swollen on palpation and is frequently tender to pressure The skin may be reddened glossy dry or moist and clammy the subcutaneous tissue edematous and the nutrition of the nails defective

Prognosis —The extent of injury and the character of the underlying lesions determine prognosis Minor degrees of trauma produce only temporary disability if the cause can be removed Accidental introduction of chemicals may produce irrecoverable lesions The neuritis produced by adjacent osteo arthritis can usually be cured whereas that consequent to caries cannot

Treatment —Neuritis due to trauma may produce a permanent physiologic interruption in the nerve and can be treated only by such surgical procedures as resection and suture Conditions which follow compression are likewise treated surgically by removal of the cause and in addition by neurolysis Causalgia may finally require injection of 60 per cent alcohol into the nerve In other types of neuritis the underlying cause (arthritis etc.) must be treated Proper splinting to prevent overstretching of paralyzed muscles and contractures should be applied The general treatment is the same as that for multiple neuritis

Multiple neuritis, polyneuritis or peripheral neuritis is an acute or subacute disseminated inflammation or degeneration of symmetrically distributed nerves which affects principally their distal portions

Incidence —It is a comparatively uncommon disease although rarely a widespread epidemic may occur, like that which resulted from arsenic poisoning among beer drinkers in England and from lead poisoning among children in Australia The two sexes are equally affected Multiple neuritis is most frequent in the second third and fourth decades of life Nondiphtheritic polyneuritis in children is rare Thomas and Greenbaum who reviewed the literature in 1007 found 138 cases and added eight The aged are sometimes affected with senile or atheromatous polyneuritis

Etiology —The causes may be grouped as toxic, infectious, and unknown Among the most common *exogenous toxins* are alcohol lead arsenic coal tar products carbon monoxide nitrobenzol mercury copper zinc phosphorus silver emetine apiol and thallium The *endogenous toxins* develop during diabetes and the cachexia of tuberculosis and syphilis Deficiency diseases such as beriberi pregnancy and perhaps alcoholism often cause polyneuritis The *infectious diseases* which most often play an etiologic role are diphtheria influenza typhoid fever measles scarlet fever whooping cough puerperal fever septicemia parotitis gonorrhea and syphilis Focal infections in the mouth or sinuses are responsible for some cases There are in addition various unknown factors

Suggestive proof has been adduced that in most cases of neuritis associated with alcoholism and diabetes or with arsenic lead and carbon monoxide poisoning a deficiency factor is the ultimate cause This proof consists of the amelioration of polyneuritis by thiamine chloride and studies upon pyruvic acid metabolism

Although marked improvement and often recovery follow the use of thiamine chloride alone it is felt that a multiple vitamin deficiency is responsible for many of the nervous system lesions which are common in beriberi pellagra polyneuritis associated with many morbid conditions such as alcoholism pregnancy diabetes gastro intestinal disturbances diphtheria and others

Such multiple deficiencies result not *only* from restriction of dietary intake but also from conditions that interfere with the utili

nign and vary in size from that of a pea to that of a child's head They may be relatively soft or very hard Multiple true neuromata have been observed chiefly in children They have been distributed in the peripheral part of the body under the skin They are very numerous in Bruns' case 100 were counted The patients otherwise are quite well

The *false neuromata* are tumors which originate in the perineurium epineurium or endoneurium They may be neurofibroma neurosarcoma, neuromyxoma etc Although they develop on all the nerves the spinal are those chiefly affected Their etiology is obscure Usually they develop in the first half of life and in many instances have been hereditary In multiple false neuromata (general neurofibromatosis) large numbers of tumors form on many or all of the peripheral nerves. R W Smith has reported a case in which 450 were counted on one extremity and 2000 were present on the body All types—plexiform neuromata pachydermatocele or elephantiasis neuromatosa and multiple neuromata neurofibromata or molluscum fibrosum (von Recklinghausen's disease) as well as tubercula dolorosa—are expressions of the same abnormal tendency These lesions may be associated with pigmentation of the skin in the form of freckles blotches or diffuse areas

The most prominent *symptom* is pain which radiates from the tumor to the periphery of the nerve. It is usually intermittent but may become continuous and agonizing Paresthesia is occasionally observed weakness is rare and the deep reflexes are seldom affected

The only available *treatment* is excision although Ludwig Kenez reported that the hypodermic administration of fibrolysin produced successful results

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DISEASES OF THE CEREBRAL NERVES

PERIPHERAL AND CENTRAL DISTURBANCES IN FUNCTION

THE OLFACTORY APPARATUS

BEFORE any conclusions can be drawn concerning the acuity of smell careful local examination of the nasal fossae is necessary The essential oils (lemon wintergreen peppermint and clove) may be employed to test the sense of smell first in one nostril and then in the other

Organic Hyposmia and Anosmia —Organic hyposmia or anosmia is the result of various conditions The sense of smell may be diminished or lost if the free endings of the nerve cells in the olfactory epithelium are involved by alterations in the nasal mucous membrane These changes may be caused by coryza influenza or diphtheria by lesions of the fifth nerve producing trophic changes in the mucous membrane by caries of the underlying supporting osseous tissue (ethmoid sinusitis) or by the growth of nasal polypi Pressure on the olfactory neurons at any point between their peripheral distribution in the nasal mucous membrane and their incorporation into the hemispheres may in

neuritis and is distinguished by the general symptoms of intoxication gastro intestinal disturbances puffiness of the lids dermatitis, hyperkeratosis changes in the nails jaundice and other evidences of hepatic disease Muscular tenderness is especially common and the changes in the muscles often lead to severe contractures of the toes and fingers Poisoning may follow administration of medicinal drugs contamination of food and drink or accidentally ingestion of vermin destroying mixtures *Lead neuritis* is often associated with the general signs and symptoms of lead poisoning a lead line' in the gum margins secondary anemia stippling of erythrocytes and abdominal pain and constipation The neuritis is frequently confined to the upper extremities Sensory changes rarely are present Intoxication results from the handling of lead products (paints type lead pipe) the smelting of ores the contamination of water and the use of cosmetics *Diphtheritic paralysis* is frequently associated with dysphagia regurgitation of fluids and nasal speech Paralysis of the ocular accommodation reflex is very common When the polyneuritic symptoms occur in the extremities they are often associated with ataxia This may at times be present without paralysis Rarely recurrent polyneuritis has been described

The course of the disease varies with the intensity of the underlying lesions As a rule the symptoms increase during the first four to six weeks and then diminish While the disease is progressing the sensory symptoms are particularly prominent The paralysis disappears later than the disturbances of sensation At times contractures develop as the result of the paralyses

Diagnosis is not difficult The disease is differentiated from *tabes dorsalis* by the acute onset the absence of Argyll Robertson pupils and bladder disturbances and the presence of paralysis Serologic findings in the spinal fluid are pathognomonic in tabes Multiple neuritis is differentiated from *anterior poliomyelitis* by the massive paralysis in the latter disease this gradually recedes in the former the motor disability gradually increases The absence of sensory changes and the asymmetric distribution of paralysis as well as the very late changes in reaction to electric stimulation in anterior poliomyelitis, are further means of differentiation There is a remote similarity between multiple neuritis and progressive muscular atrophy the dystrophies periarteritis nodosa, polymyositis, acrodynia and hysteria

Treatment —The first step in the treatment of multiple neuritis is to be remove the cause Elimination of some of the metallic poisons may be favored by administration of potassium iodide catharsis and sulfur baths Sodium thiosulfate may be given for arsenic polyneuritis

In the endogenous types of polyneuritis Oppenheim used diaphoresis If the patient s strength permits the secretion of sweat may be stimulated by hot baths otherwise by hot packs or hot air applications and hot drinks and aspirin A strengthening diet is necessary in all forms of neuritis The close relationship of polyneuritis to avitaminosis has led to many quick recoveries following the oral intravenous or intramuscular use of vitamin B_1 A daily dose of 100 to 200 mg of thiamine chloride intramuscularly is a popular method of administration Artificial hyperpyrexia has also been valuable

The *pain* may be relieved by warm fomentation or antineuralgic drugs General tonic medication may be prescribed—cod liver oil iron quinine and strychnine During the first stages of the disease absolute rest in bed is imperative Proper splints must be applied to prevent contractures and over stretching of the paralyzed muscles When the condition has become stationary or shows the first signs of improvement physiotherapy consisting of massage passive movements gradually increasing resistive exercises and electrotherapy is necessary Subcutaneous injection of strychnine is useful in persistent paralysis Residual paralysis and contractures must be treated surgically

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NEUROMATA

Nearly a century ago Odier recognized that tumors may grow from nerves Neuromata have been classified according to Virchow as true and false *True neuromata* are tumors arising from or composed of actual nervous tissue They are exceedingly rare and are found practically only in connection with the sympathetic system They are be-

companied by other congenital defects such as deafness deficient intelligence and sometimes by cataract and other visual disorders. The condition appears in early life and becomes progressively more marked In the early stages it is manifested by night blindness (nyctalopia) and by concentric contraction of the fields of vision The progressive diminution of vision rarely results in complete blindness

SECONDARY RETINITIS—(*a*) RETINITIS SECONDARY TO RENAL DISEASE.—According to Gowers there are three fairly well differentiated types of retinal change in nephritis (1) degenerative, (2) hemorrhagic (3) inflammatory

In the degenerative type widespread evidence of degeneration appears throughout the retina without any change in the disk The toxic character of this type of alteration is permanent and the retinal elements suffer an almost direct selective destruction In the hemorrhagic type there is only slight evidence of inflammation and the extravasations may be flame shaped and extend over a considerable part of the retina or linear and remain closely confined to the region of blood vessels These lesions are usually associated with evidence of marked arteriosclerosis in the fundus In the inflammatory form there are marked retinal changes characterized by edema areas of exudate and hemorrhage engorgement, dilatation and tortuosity of the blood vessels and an obscuration of the margins of the disk with an actual papilledema which may amount to four or five diopters of swelling These alterations produce an appearance of the disk which is practically identical with that found in increased intracranial pressure.

Although retinal changes occur in the course of both acute and chronic nephritis they are more commonly associated with interstitial nephritis In all conditions suspected of having a renal basis the eyegrounds should be carefully examined as there is often no apparent relationship between the extent of renal involvement and the manifestations in the fundus Retinitis may also appear as a symptom of the general toxemia of pregnancy This type of disturbance usually clears up after delivery

(*b*) RETINITIS SECONDARY TO SYPHILIS.—The retinitis secondary to syphilis has been described as occurring in acquired syphilis but it more usually accompanies the inherited type. The primary inflammation seems to be in the choroid while the retinal changes appear to be secondary manifestations with extensive accumulations of black and brownish pigment between the retinal elements The process usually results in a considerable thinning of the retina and the choroid which materially increases the translucency of the retina so that the choroidal vessels are easily seen through it The accumulations of pigment may be excessive

(*c*) RETINITIS SECONDARY TO HEMAL DISTURBANCES —The retinal changes associated with anemia, malaria leukemia and other general diseases such as diabetes purpura chronic lead poisoning and so forth are principally the results of alterations in the constituents of the blood

In primary and secondary anemia leukemia purpura and at times in metabolic disturbances such as diabetes there is a marked tendency to the occurrence of hemorrhages throughout the body When these occur in the retina they are frequently followed by thickenings which result in scarring and thus disturb the function of the visual elements

(*d*) RETINITIS SECONDARY TO DEGENERATION OF THE CENTRAL NERVOUS SYSTEM.—Amaurotic family idiocy is manifested by progressive loss of sight, resulting in complete blindness and by increasing idiocy The more common type appears in infancy and is usually limited to Russian or Polish Jews In early stages the macular region is found to be definitely pale and atrophic as the condition progresses a cherry red spot appears in the center of the macula. This lesion is associated with widespread degeneration of the entire nervous system which finally causes death

The less common type of amaurotic family idiocy appears in adolescence and is much less severe It does not always result in complete blindness or dementia.

In both types of the disease not only the visual fibers but also the light fibers of the retina are affected and the reaction of the pupils to light accommodation and convergence is disturbed Localized mono homonymous losses of vision (scotomata)

terfere with the conduction of olfactory stimuli Meningeal thickening neoplasms which arise from the floor of the anterior cranial fossa or in the frontal lobes and press on one or both olfactory tracts abscesses hemorrhages areas of softening near the olfactory pathways or any general increase in intracranial pressure may reduce or destroy the sense of smell Laceration of one or both tracts the result of fracture of the floor of the anterior cranial fossa, may produce unilateral or bilateral hyposmia or anosmia

Alterations in the mucous membrane or changes in the nerve endings frequently produce a reduction in the sense of smell in persons who are engaged in the handling of wine of cognac in those who smoke to excess and in individuals addicted to cocaine by inhalation Senile changes in the mucous membrane also reduce the acuity of the sense of smell

Parosmia a perversion of the sense of smell may be a symptom of generalized cerebral disease or it may be an indication of local functional disturbance in the olfactory lobe Such perversions are usually of an unpleasant character Hallucinations of smell frequently occur as the result of disorders of the olfactory cortex They take place frequently in the aura of approaching convulsive seizures and constitute a variety of attack known as the hippocampal convulsive state They occur frequently in the insane

Neoplasms arising in the uncus produce a definite syndrome characterized by extreme olfactory hallucination—usually unpleasant rarely pleasant—and by generalized convulsive seizures or localized tremors and twitchings which have been ascribed to pressure on the red nucleus There is frequently also a homolateral exophthalmos with marked venous engorgement due to pressure on the cavernous sinus and occasionally the oculomotor nerves which lie in the wall of the sinus are involved Pressure on the brain stem may in addition evoke other signs of involvement of the central nervous system These manifestations are usually accompanied by the general signs of increased intracranial pressure

Functional—Hysteric anosmia is often associated with similar disturbances in the other special senses and also in general body sense Its distribution is usually unilateral and all of the disturbances both motor and sensory almost invariably affect the same side of the body Hyperosmia—increased acuity of smell—is a variable and indefinite condition which is usually a symptom of hysteria

HENRY ALSOP RILEY

THE VISUAL APPARATUS

Strictly speaking the peripheral portion of the optic apparatus is an intrinsic part of the brain and is not homologous with the peripheral cerebral or spinal nerve

The visual receptors in the retina and the central processes which pass from them to the deeper layers of the retina are the only homologs of the peripheral nerves in the optic apparatus

The visual structures from the retina to the thalamic centers represent the derivatives from an evagination of the primitive neural tube.

Extraneural Factors in Visual Defects—Extraneural disturbances in vision may result from pathologic changes in the various media of the eye Disorders of vision produced by such causes may be identified by proper methods of examination

Retinal Factors in Visual Defects—Retinitis may be a disease of the retina itself or the expression of some degenerative systemic or neural disease which expresses itself by changes in the retina These alterations may result in all kinds of visual disturbance

PRIMARY RETINITIS.—In primary or simple retinitis the evidence of inflammation is limited to swelling of the retinal element distention of the blood vessels and occasional hemorrhages This condition is considered by some authorities to be the first stage of the more advanced forms but by others it is thought to be a definite type which may not undergo any further development Overuse of the eyes uncorrected errors of refraction poor illumination exposure to cold or to excessive light may produce this type of retinitis

RETINITIS PIGMENTOSA may appear as a definite and specific disease *sui generis* not associated with syphilis It usually is hereditary and is often found in the offspring of consanguineous parents It is frequently ac

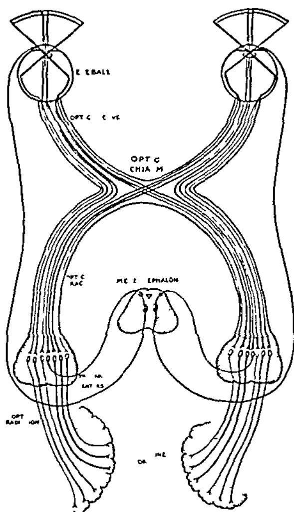


Fig 192—The visual pathway This diagram indicates the reversal of the visual and retinal fields the course of the fibers which arise from the various portions of the retina, and the path of the light reflex Red indicates the temporal fibers Blue indicates the nasal fibers Green indicates the macular fibers Black indicates the light fibers The uncrossed course of the temporal fibers, the crossed course of the nasal fibers and the partially crossed and partially uncrossed course of the macular fibers are indicated The primary visual centers consisting of the pulvinar of the thalamus and the lateral geniculate body are indicated together with the course of the optic radiation to the calcarine cortex The switching of the light reflex stimulus from the primary visual centers to the tectum of the midbrain and its connection with the efferent oculomotor neuron governing the sphincter iridis is also shown

result from local destruction of the visual elements They are appreciated by the patient as dark spots in the field of vision

Neural Factors in Visual Defects.—Neural causes of visual defects are of two types those which interfere with the visual pathways and those which disturb the cortical perceptive system The disturbances in vision which result from localized processes affecting the visual pathways manifest themselves clinically according to the particular anatomic part of the apparatus which they involve In considering the defects of vision which result from local lesions it is essential to remember the anatomic arrangement of the fibers which constitute the various parts of the visual pathway from the eyeball to the cortical centers In differential diagnosis the fact that the optic nerve and tract contain both light and sight fibers is of importance Both types of fibers remain commingled as far caudad as the primary visual centers consisting of the pulvinar and the lateral geniculate body Emerging from these nuclei the visual fibers form the optic radiation (radiation of Gratiolet), while the light fibers pass to the superior colliculus and form a part of the reflex arc which controls the retinal illumination It is this arrangement which renders possible the pupillary reactions of Wernicke A lesion affecting the visual pathway between the chiasm and the primary visual centers produces a contralateral homonymous hemianopsia through the interruption of the fibers arising from the temporal retina of the homolateral eye and the nasal retina of the contralateral eye This disturbance affects equally the visual and the light reflex fibers and a narrow beam of light falling upon the parts of the retina rendered blind by the lesion will not result in a light reflex If however the cause of the disturbance affects the visual pathway caudal to the primary visual centers at which point the light and sight fibers separate the patient will present an homonymous hemianopsia but the light reflex from the affected portion of the retina will be retained These reactions are difficult to demonstrate but are of considerable localizing value when present

Disturbance of Vision Due to Local Factors.—LESIONS OF THE OPTIC NERVE.—The conduction of impulses over the fibers of the optic nerve may be interfered with by local injury or disease involving the nerve within the orbit, in the optic foramen or between the optic foramen and the optic chiasm Laceration of the nerve may result from fracture of the base of the skull involving the walls of the orbit, the anterior cranial fossa or the most anterior portion of the middle cranial fossa Neoplasms arising in the orbital cavity from the contents of the orbit or from the periosteum or bone of the wall of the orbit or optic foramen may compress the optic nerve. Tumors arising in the caudal portion of the orbital gyrus of the frontal lobe may by impinging directly on one or both optic nerves, interfere with vision As a result of the pressure exerted directly on the nerve there is usually evident a primary atrophy in the nerve head and a reduction in vision commensurate with the atrophy while papilledema appears in the fundus Optic atrophy may result from primary tumors of the optic nerve (gliomata) tumors of the nerve sheath (neurofibromata and sarcomata) and from involvement by metastatic neoplasms Compression of the optic nerves may also result from acute or chronic inflammation in the periosteum or walls of the optic foramen Periostitis or osteitis is usually caused by chronic infections such as syphilis and tuberculosis Osteitis deformans and leontiasis ossea may produce sufficient overgrowth of the bone forming the optic foramen to compress the optic nerve and thus produce partial or complete loss of function

Inflammation of the contents of the orbit either hematogenous or by direct extension from the eyelid or accessory nasal sinuses may produce an optic neuritis with diminution or loss of vision in one eye Involvement of the optic nerve by local toxic or inflammatory processes usually manifests itself as an increasing central scotoma, the more vulnerable macular fibers being the first to be disturbed A frequent source of this type of involvement is an inflammation of the ethmoid cells

LESIONS OF THE OPTIC CHIASMA may result from disorders of the hypophysis the hypencephalon the bony tissues of the sella turcica the blood vessels or the meninges in its vicinity The inflammatory processes

which may affect the chiasma are usually direct extensions from an inflammation of the sphenoidal sinus or from localized meningitic processes Lesions affecting the central portion of the chiasma involve the fibers which cross from the nasal half of each retina to the opposite side. This results in a loss of function in the nasal halves of the retina of both eyes (bitemporal hemianopsia) The lesion which most often produces this visual disturbance is an hypophyseal neoplasm In many instances the involvement of the chiasm may be asymmetric, the neoplasm extending more to one side and may involve *one entire optic nerve producing an amaurosis* in the eye on that side and temporal hemianopsia in the other eye A relatively unusual type of involvement of the chiasma is an aneurysm or varicose dilatation of one or both carotid arteries compressing the chiasma from one or both sides An involvement of this kind impinging upon the lateral aspects of the chiasma interrupts the uncrossed fibers from the temporal half of each retina and produces a binasal hemianopsia

Lesions of the Optic Tract—The causative factors producing disturbances in the optic tracts are similar to those already mentioned namely injuries softening from vascular lesions neoplasms from the base of the skull or from the meninges localized meningitic processes or intracerebral neoplasms which press on the optic tract in its course toward the primary visual end stations the lateral geniculate body and the pulvinar of the thalamus Involvement of the tract in this locality produces a contralateral homonymous hemianopsia with corresponding loss of the light reflex

Lesions of the Primary Visual End Stations—The primary visual end stations in the thalamus and methalamus consist of the lateral geniculate body and the pulvinar of the thalamus Lesions of these structures are usually due to inflammatory processes vascular disease (embolism thrombosis hemorrhage) or neoplasms These disorders produce a contralateral homonymous hemianopsia usually accompanied by other disturbances such as partial or complete contralateral hemianesthesia or hemiplegia Vertical gaze may also be paralyzed by a disturbance in the subthalamic aberrant pyramidal bundle which supplies the nuclei of the third nerve From the primary end stations the visual pathway passes through the retrolenticular portion of the internal capsule and the corona radiata to the calcarine cortex

The optic radiation in the occipital lobe of the hemisphere may be involved by neoplasms arising from the brain itself the meninges overlying the brain or from the skull by vascular disease (hemorrhage embolism or thrombosis) by diffuse or local inflammation (encephalitides brain abscess) and by degenerative or sclerotic processes These disorders produce an homonymous hemianopsia *the light reflex from the affected* retinal fields being preserved Lesions in the temporal lobe which affect only a portion of the optic tract may produce sector deformities in the visual fields

Lesions of the Calcarine Cortex—Lesions of the cuneus produce a contralateral homonymous hemianopsia Bilateral disease of the cunei may cause complete blindness This involvement of both occipital lobes may result from degenerative sclerotic inflammatory, neoplastic or vascular disorders which are bilaterally symmetric from pressure by new growths originating in the falx cerebri between the occipital lobes or from trauma

Transient hemianopsia usually of the homonymous types is not uncommon in the ophthalmic type of migraine It may be associated with the scintillating scotomata which are often found in this disease. These disturbances probably depend upon transient interruptions of the circulation

Disease of the meninges or bone overlying the lateral aspects of the occipital lobes such as inflammation or neoplasms injury producing a laceration of this part of the brain as well as degeneration or sclerotic processes and vascular accidents inflammations and intrinsic new growths of the occipital lobe may interfere with the higher associative functions of this part of the brain although the perception of the primary visual qualities of form color etc is intact This condition is called mind blindness The higher psychic elaboration of the primary visual constituents is lost and although the patient is still able to see he cannot appreciate the meaning and significance of objects He is no longer able to

DIFFUSE NEURITIS involving the entire optic nerve causes marked amblyopia or blindness It is often associated with acute myelitis and develops in the course of infectious diseases particularly influenza and syphilis and in conjunction with scarlet fever malaria yellow fever and erysipelas Diffuse optic neuritis may also accompany epidemic encephalitis It may become so severe that a papilledema of four or five diopters of swelling results This is indistinguishable locally from the optic neuritis with papilledema which is evoked by increased intracranial pressure. The cause of this encephalitic papilledema is thought to be a leptomeningitis which occludes the foramina of exit of the cerebrospinal fluid and thus produces an internal hydrocephalus

ASSOCIATED DEGENERATIVE CONDITIONS OF THE CENTRAL NERVOUS SYSTEM —OPTIC NEURITIS OR OPTIC ATROPHY may appear in the course of multiple sclerosis It is a very common evidence of this disease and is usually confined to the temporal halves of the disks which are markedly pale It frequently appears also in tabes dorsalis general paresis Friedreich s and Marie s ataxias

MYASTHENIA GRAVIS may produce a concentric constriction usually more or less transient of the visual fields. This may progress during the active course of the attack and then regress as the other symptoms of the disease disappear More often however myasthenia gravis produces a transient diplopia or ptosis from involvement of the oculomotor nerve

Postneuritic secondary or inflammatory optic atrophy usually follows papillitis or neuritis retinitis or pigmentary degeneration of the retina embolism of the central artery glaucoma or trauma The disk has a dense white or grayish color with more or less irregularity and obscuration of the margin The minute vessels disappear completely and the lamina cribrosa is hidden by the organized exudate. The retinal arteries are narrow show a white line and the veins are enlarged and tortuous After injury to the nerve atrophy may not appear for several weeks although vision is immediately diminished or lost A surprising amount of vision may remain after optic neuritis or optic atrophy In differentiating between a papillitis and a papilledema the degree of retention of vision may be of some aid it is always much greater in the latter than in the former condition although the appearance of the disk may seem to be almost identical

HYSTERIC AMBLYOPIA may be unilateral or bilateral The narrowing of the visual fields increases characteristically during examination The extent of the visual fields varies greatly from time to time and the color fields may be inverted It is usually accompanied by other evidences of the hysteric condition

PAPILLEDEMA is usually the result of an increase in intracranial pressure caused by intracranial neoplasms or internal hydrocephalus Intracranial neoplasms may arise from the cerebral tissue itself from the meninges or from the skull The presence of this addition to the normal intracranial contents increases the pressure within the skull and presses the tissue fluid into the various exits from the intracranial space The perineural sheaths of the optic nerves participate in this general distention and papilledema develops. In the early stages there is usually only an increase in the diameter of the veins As the pressure continues to increase however the veins become tortuous and the margins of the disks indistinct Radial lines appear which extend from the center of the papilla over the edge of the disk into the retina and the retina itself begins to participate in the edema The edema increases and the papilla becomes raised above the level of the surrounding retina There is a consequent obliteration of the normal physiologic cup the vessels pass across the disk and then dip over the edge to reappear as they traverse the retina The degree of swelling of the disk is measured by determining the lens in the ophthalmoscope with which the details of the retina can be most distinctly seen and then carrying out the same procedure focusing upon the summit of the papilla The actual swelling is computed by subtracting the two lens numbers the result being expressed in diopters each one equaling ⅓ mm Hemorrhages and patches of localized exudate become evident at this stage scattered throughout the retina If the cause for the increased intracranial pressure be removed recession may

recognize objects by name and there is no understanding of their uses The meaning of written and printed words is affected also

General Causes of Disturbance of Visual Function—The general factors bringing about disturbance of vision are the exogenous and endogenous toxemias and the degenerative conditions associated with disease of the central nervous system

Exogenous Toxins—The excessive use of tobacco may produce a gradual progressive diminution in the central fields of vision This is first evidenced by the inability to recognize red and green (a central scotoma for red and green) If the intemperate use of tobacco continues a complete optic atrophy with total loss of sight (unilateral or bilateral) may result in exceptional cases Similar involvement of the optic nerve may follow poisoning by the heavy metals particularly lead and by methyl alcohol and also by quinine in individuals who are hypersensitive to this drug Hemeralopia (day blindness) in which the patient sees better in a dim light is not uncommon in these amblyopias of exogenous origin

Endogenous Toxins—Diminution of vision is sometimes associated with severe or repeated infection of the respiratory tract, as well as with syphilis tuberculosis diabetes, typhoid fever, erysipelas influenza, pneumonia tonsillitis, malaria, beriberi, the toxemia of pregnancy and extensive cutaneous burns

Results of Both Endogenous and Exogenous Intoxications—The result of endogenous and exogenous intoxications is an optic neuritis of three types axial interstitial or peripheral and diffuse Axial neuritis (neuritis of the papillomacular bundle) affects the optic nerve between the eyeball and the optic chiasma It may be acute or chronic The acute type appears in young adults particularly in females It is usually manifested by a sudden cloudiness or diminution of vision with frontal headache and orbital pain which is increased by pressure on or movement of the eyeballs The loss of vision is rapid and usually reaches its maximum in a short time With the loss of sight the headache diminishes Usually no change can be seen by ophthalmoscopic examination The pupil of the affected eye is larger than the other and as a rule contracts on direct stimulation, but quickly dilates despite continued stimulation After the acute stage there is gradual recovery of sight at the periphery, although varying degrees of central scotoma may persist The permanent visual defect may be unilateral or bilateral, may affect only color, or may be limited to central or paracentral scotoma *The chronic form* is more common and is usually associated with chronic alcoholism and nicotine poisoning The condition often begins with red green scotoma In the earliest stages it may be recognized by the difference between the appearance of red and green in the peripheral and central fields of vision Acuity of vision gradually diminishes The fundus may be entirely normal or may appear hyperemic or mildly neuritic with some temporal pallor The prognosis depends on the severity of the involvement The characteristic lesion is a degeneration of the papillomacular bundle This may in severe cases become complete with a unilateral or bilateral optic atrophy

An hereditary form of axial neuritis is described which seems to affect males and is transmitted by unaffected females (von Leber s atrophy) It progresses acutely or subacutely Its incidence is manifested by a central scotoma which affects color vision before perception of form and gradually increases in size Nyctalopia (night blindness) is a common symptom Total blindness results in about 33 per cent of cases The fundus shows an optic atrophy which is most marked in the temporal half of the disk This disease is rare

Interstitial or peripheral neuritis in contrast to axial neuritis, involves the periphery of the optic nerve before the papillomacular bundle is involved and results in a concentric limitation of the field of vision for white instead of producing a central scotoma for colors Central vision usually remains sharp even for color Ophthalmoscopic examination reveals a simple or neuritic atrophy Very occasionally the evidences of papilledema appear This type of neuritis usually follows systemic infections such as measles diphtheria influenza typhoid fever syphilis diabetes the meningitides disease of the nasal sinuses and metallic poisoning (lead and arsenic)

take place with organization of the patches of exudate and of the hemorrhages The edge of the disk never, as a rule, returns completely to normal but remains blurred because new connective tissue has formed by the organization of the inflammatory exudate The end result of a papillitis may be a return to normal optic atrophy with the retention of a considerable degree of visual acuity but with concentric contraction of the visual field or blindness from the postneuritic atrophy Papilledema may also be associated with echinococcus cysts, cysticercus cellulosae brain abscess lues tuberculosis, hydrocephalus, sinus thrombosis nephritis lead encephalopathy, leukemia, epidemic encephalitis and pachymeningitis hemorrhagica.

Chromatopsia is the ability to recognize colors Achromatopsia or color blindness, may appear as an hereditary or acquired defect in vision In the hereditary form it may occur as a loss of the ability to distinguish red and green the individual being able to recognize the blue yellow combinations (partial achromatopsia) or it may involve all colors (complete achromatopsia) It usually affects both eyes Acquired achromatopsia may follow extensive disease of the retina or of the optic nerve

Visual perversions may appear without apparent change in the retina or the optic nerve The most frequent is red vision (erythropsia) which appears after cataract extraction The excessive use of santonin as a vermifuge may disturb the color vision The first bluish tinge is later replaced by a yellowish discoloration (xanthopsia) which renders blue objects greenish and violet objects indistinct No satisfactory explanation of these visual disorders has been found

Henry Alsop Riley

THE OCULOMOTOR APPARATUS (THIRD, FOURTH AND SIXTH NERVES)

Lesions of the Oculomotor Nuclei and the Efferent Fibers of the Oculomotor Nerves—Nuclear lesions of the oculomotor nerves result from the acute encephalitides associated with infectious diseases such as measles scarlet fever chickenpox smallpox, or influenza with acute epidemic encephalitis and polioencephalitis and with chronic inflammatory or degenerative diseases as chronic anterior poliomyelitis chronic nuclear encephalitis progressive nuclear degeneration, ascending spinal paralysis, amyotrophic lateral sclerosis, multiple sclerosis syringobulbia tabes and cerebrospinal syphilis The hemorrhagic polioencephalitis of Wernicke a rapidly developing disease, involves almost selectively the nuclei of the oculomotor nerves It usually spares the internal muscles of the eye It is characterized by headache vertigo vomiting and progressive involvement of the oculomotor nerves A much less well defined group of diseases including paralytic vertigo, exophthalmic goiter pseudoparalytic myasthenia, myasthenia gravis, and ophthalmoplegic migraine may evoke oculomotor palsies of various types

Disturbances of the oculomotor apparatus are frequent in severe migraine (so called 'ophthalmoplegic migraine") These interferences with function appear after the acute attack as paretic or paralytic sequelae usually involving the third cerebral nerve although infrequently the fourth or sixth nerve may be affected This condition is analogous to weakness sometimes found in one or both extremities of one side or the other after convulsive attacks but is considered to be the result of organic pathologic conditions in the vicinity of the nerves

The nuclei may also be involved in vascular disease hemorrhage thrombosis or embolism of the small vessels which supply the oculomotor trochlear and abducens nuclei With these forms of vascular disturbance the pyramidal tract is frequently involved Involvement of the pyramidal tract and the homolateral oculomotor nerve produces the superior alternating type of hemiplegia, while a disturbance of the pyramidal tract and the homolateral abducens nerve results in the middle alternating hemiplegia

The oculomotor and trochlear nuclei may be affected by pressure exerted by neoplasms arising in the vicinity The usual sites of origin are the collicular plate the pineal gland the tegmentum of the mesencephalon the caudal portion of the thalamus or the interpeduncular region The abducens nucleus may be involved by neoplasms arising in the pons the cerebellopontile angle the

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posterior longitudinal fasciculus usually appear as interruptions in the conjugated movements of the two eyes together, the assumption of bizarre attitudes (skew deviation) or paralyses of conjugate gaze.

Inflammation degeneration injury, vascular accidents, and destructive neoplastic activity involving the posterior longitudinal fasciculus may result in a destruction of the fibers linking the oculomotor trochlear and abducens nuclei in the conjugated movements of the eyes or may cause interference in conjugate gaze by affecting the fiber tracts descending from suprasegmental centers to their nuclei

Disturbances in the vestibular and cerebellar control of the eyeballs occasioned by lesions of the posterior longitudinal fasciculus appear as abnormal ocular movements called *nystagmus* This is an oscillatory movement of the eyes which is of three types vestibular cerebellar and congenital In *vestibular nystagmus* the movement of the eyes is divided into a slow and a rapid phase The slow phase is a drifting away of the eyes from the point of fixation because of vestibular influence while the rapid phase is the voluntary return of the eyes to the point of fixation This type of nystagmus is most easily seen in extreme lateral gaze but may sometimes be demonstrated in vertical gaze (vertical nystagmus) *Rotary nystagmus* is due to abnormal activity of the oblique muscles *Cerebellar nystagmus* which usually accompanies all movements of the eyeballs or fixation of the eyes is a true asynergia of gaze which results in unbalanced activity of the muscular apparatus due to disturbed cerebellar control In *congenital nystagmus* the eye movements are in wild disorder quite extensive irregular and follow no definite pattern Nystagmus may also result from extensive retinal disease

The nystagmus due to imbalance of the ocular muscles is most commonly seen in multiple sclerosis but also develops in myasthenia gravis Friedreich s ataxia alcoholism individuals with congenital mental defects and in miners who must work in a poor light with their heads in abnormal positions It may be produced by mechanical irritation of the semicircular canals rotation and stimulation by electricity or by the injection of cold or hot water into the external auditory meatus

Disturbances in Conjugate Movements —Supranuclear disease of the oculomotor pathways causes disturbances of the conjugated movements of the two eyes Lesions producing interference with conjugate gaze may be situated in the oculogyric centers in the lower part of the intermediate precentral region of the cortex, along the fiber tracts conducting these impulses or in the brain stem centers for vertical or lateral gaze or for convergence or divergence In the disturbances of lateral gaze if the lesion be irritative the action of the affected muscles is increased and the patient looks away from the side of the lesion if however the involvement causes a paralysis of gaze the unopposed action of the antagonistic muscle groups results in the gaze being directed toward the side of the lesion Disturbance of lateral or vertical gaze may result from lesions of the aberrant pyramidal system Paralysis of vertical gaze is often associated with disease of the colliculi or of the pineal gland It is uncertain whether the paralysis of vertical gaze which is present often in pineal tumor is the result of pressure by the neoplasm upon the superior colliculi the oculomotor nuclei or a hypothetic center for vertical ocular movements situated in close proximity to the oculomotor nuclei It may also result from an involvement in the subthalamus of the aberrant pyramidal bundle controlling vertical movements

Paralysis of conjugate movements has been said to occur in *exophthalmic goiter* as a manifestation probably of the general toxemia In hyperthyroidism the exophthalmos may be so extreme as to produce a complete mechanical external ophthalmoplegia due to stretching of the muscles The reactions of the pupils to light and accommodation are usually not affected

Hysteric ptosis may simulate disease of the third nerve On passive elevation of the lid however there is no evidence of association of other ocular palsies which almost invariably accompany the ptosis of the organic lesions In hysteria any attempt to raise the lid with the finger evokes resistance which is never present in paralytic ptosis Hysteric ptosis is also accompanied usually by other hysteric stigmata

Exophthalmos is usually found in exophthalmic goiter and is accompanied by other ocular manifestations the sign of von Graefe i.e. slow and imperfect following of the movement of the eyeball by the eyelid the sign of Stellwag a widening of the palpebral fissure, and the sign of Moebius a weakness in the power of convergence Exophthalmos frequently accompanies pronounced myopia It is frequently found unilaterally in association with arteriovenous aneurysm of the cavernous sinus and with disease of the contents of the orbit or the bony tissue forming its walls If the exophthalmos be the result of systemic disease it is usually bilateral if it results from local abnormalities it is usually unilateral It may be so marked as to interfere with proper closure of the eye (lagophthalmos) and result in a keratitis the consequences of which may be serious

Enophthalmos is due to disease of (1) the oculopupillary center in the medulla (2) the ciliospinal center in the spinal cord or (3) the preganglionic fibers which originate in the ciliospinal center pass to the vegetative nervous system and reach the ciliary ganglion It may also follow disease within the orbit or loss of orbital tissue It is almost always unilateral

HENRY ALSOP RILEY

THE TRIGEMINAL NERVE

It has for a long time been a question for debate whether the sense of taste belongs to the trigeminal or to the facial nerve but the greater weight of evidence seems to indicate that it is an essential function of the seventh cerebral nerve The distribution of the taste fibers is merely taken over by the trigeminal nerve A discussion of the disturbances in taste is therefore included in the consideration of the seventh cerebral nerve

Diminution in Sensibility of the Trigeminal Nerve (*Hypesthesia or Anesthesia*) —The trigeminal nerve supplies sensation to the skin of the face the anterior half of the scalp the mucous membrane of the lips mouth tongue and pharynx the accessory spaces of the nose the teeth portions of the dura mater and the cornea and conjunctiva of the eye Disturbances in sensation may be partial (hypesthesia) or complete (anesthesia) If complete they may include all types of sensibility or be merely a dissociation of sensation certain types being affected while others remain uninvolved The disturbance may also be either peripheral in type and corresponds to the distribution of the three branches of the trigeminal nerve (the ophthalmic maxillary and mandibular divisions) or segmental and limited to areas corresponding to the circumoral arrangement of the trigeminal dermatomes described by Dejerine Careful plotting of the area of disturbed sensation will indicate the peripheral or segmental character of the sensory loss

Peripheral Disturbances—An interference with the conduction of impulses by the fibers of the trigeminal nerve results in a reduction in superficial sensibility (touch pain and temperature) which may be partial or complete according to the severity of the lesion If only one of the branches of the nerve is involved the disturbance is limited to all or a part of the distribution of the branch If the root of the nerve is affected the result may be a uniform diminution of sensation over the area supplied by the entire nerve or it may present an uneven distribution The branches of the trigeminal nerve may be affected by inflammatory processes in the deeper tissues of the face or mouth by inflammatory hyperplastic or neoplastic processes affecting the bones of the skull and involving the nerves in their course through the various foramina The root of the nerve may be involved by meningitic processes by neoplasms arising from the bones of the cranial fossae the meningeal envelopes and from the pons cerebellum or acoustic nerve Neoplasms may also originate in the nerve itself or in the nerve sheath (von Recklinghausen s disease) and produce hypesthesia or anesthesia of any division or of the entire nerve according to the site of development

The divisions of the nerve may be lacerated by direct penetrating wounds or fracture of the base of the skull passing through the foramina or by tears of the dura implicating the nerve The ophthalmic division on account of its location is also exposed to damage by aneurysm of the internal carotid

posterior longitudinal fasciculus usually appear as interruptions in the conjugated movements of the two eyes together, the *assumption of bizarre attitudes* (skew deviation) or paralyses of conjugate gaze.

Inflammation, degeneration injury, vascular *accidents*, and *destructive neoplastic* activity involving the posterior longitudinal fasciculus may result in a destruction of the fibers linking the oculomotor *trochlear* and abducens nuclei in the conjugated movements of the eyes or may cause interference in conjugate gaze by affecting the fiber tracts descending from suprasegmental centers to their nuclei

Disturbances in the vestibular and cerebellar control of the eyeballs occasioned by lesions of the posterior longitudinal fasciculus appear as abnormal ocular movements called *nystagmus* This is an oscillatory movement of the eyes which is of three types vestibular cerebellar and congenital In *vestibular nystagmus* the movement of the eyes is divided into a slow and a rapid phase The slow phase is a drifting away of the eyes from the point of fixation because of vestibular influence while the rapid phase is the voluntary return of the eyes to the point of fixation *This type of nystagmus is* most easily seen in extreme lateral gaze but may sometimes be demonstrated in vertical gaze (vertical nystagmus) *Rotary nystagmus* is due to abnormal activity of the oblique muscles *Cerebellar nystagmus* which usually accompanies all movements of the eyeballs or fixation of the eyes, is a true asynergia of gaze which results in unbalanced activity of the muscular apparatus due to disturbed cerebellar control In *congenital nystagmus* the eye movements are in wild disorder quite extensive irregular and follow no definite pattern Nystagmus may also result from extensive retinal disease

The nystagmus *due to imbalance of the* ocular muscles is most commonly seen in multiple sclerosis but also develops in myasthenia gravis Friedreich s ataxia alcoholism individuals with congenital mental defects and in miners who must work in a poor light with their heads in abnormal positions It may be produced by mechanical irritation of the semicircular canals rotation and stimulation by electricity or by the injection of cold or hot water into the external auditory meatus

Disturbances in Conjugate Movements —*Supranuclear disease of the oculomotor* pathways causes disturbances of the conjugated movements of the two eyes *Lesions producing interference with conjugate gaze* may be situated in the oculogyric centers in the lower part of the intermediate *precentral region of the cortex, along the* fiber tracts conducting these impulses or in the brain stem centers for vertical or lateral gaze or for convergence or divergence In the disturbances of lateral gaze if the lesion be irritative, the action of the affected muscles is increased and the patient looks away from the side of the lesion if however, the involvement causes a paralysis of gaze the unopposed action of the antagonistic muscle groups results in the gaze being directed toward the side of the lesion *Disturbance of lateral or vertical gaze may result from lesions of the aberrant pyramidal system Paralysis of vertical gaze is often associated* with disease of the colliculi or of the pineal gland It is uncertain whether the paralysis of vertical gaze which is present often in pineal tumor is the result of pressure by the *neoplasm upon the superior colliculi the* oculomotor nuclei or a hypothetic center *for vertical ocular movements situated in* close proximity to the oculomotor nuclei It *may also result from an involvement in the* subthalamus of the aberrant pyramidal bundle controlling vertical movements

Paralysis of conjugate movements has been said to occur in *exophthalmic goiter* as a manifestation probably of the general toxemia In hyperthyroidism the exophthalmos may be so extreme as to produce a complete mechanical external ophthalmoplegia due to *stretching of the muscles The reactions of* the pupils to light and accommodation are usually not affected

Hysteric ptosis may simulate disease of the third nerve On passive elevation of the lid however there is no evidence of association of other ocular palsies which almost invariably accompany the ptosis of the organic lesions In hysteria any attempt to raise the lid with the finger evokes resistance which *is never present in paralytic ptosis* Hysteric ptosis is also accompanied usually by other *hysteric stigmata*

affects all types of sensibility is frequently complete extends with precision to the mid line and may be associated with functional anosmia ageusia and amaurosis and with other hysteric stigmata such as loss of corneal and pharyngeal reflexes The character and distribution of the changed sensations are found to be profoundly affected by suggestion

Motor disturbances of the trigeminal nerve may be irritative or paralytic

Irritative —The irritative type of disturbance is characterized by local or general spasms of the muscles of mastication It may be produced by irritative lesions in the part of the cortex which controls the masticatory muscles The hyperkinetic symptoms may constitute the manifestation of a jacksonian convulsive state Violent convulsive movements of the jaws are also seen in generalized convulsize seizures biting of the tongue being one of the most characteristic manifestations Spasm of the masticatory muscles may be an expression of more widespread irritation of the central nervous system It may be the initial symptom of tetanus or lockjaw If limited to the jaws it is called *trismus* Spasm of the masticatory muscles constitutes one of the outstanding features of *hydrophobia* It occurs in the chattering associated with chills Masticatory spasm may result from reflex irritation arising in the mouth jaws or teeth It is present also in strychnine poisoning

Other hyperkinetic masticatory manifestations appear in paralysis agitans and epidemic encephalitis In paralysis agitans the typical tremor may be located in the muscles of the jaw and cause a constant or inconstant rhythmic tremor In many of the sequelae of encephalitis there is a similar involvement Not only syndromes similar to that of pseudobulbar palsy but also irritative phenomena have been observed such as grinding champing and chattering movements This involvement of the masticatory apparatus in the chronic forms of epidemic encephalitis seems to be caused by inflammatory and degenerative lesions in the substantia nigra

Paralytic disturbances may be peripheral or central

Peripheral —Paresis or paralysis of the masticatory muscles may be a manifestation of a local neuritis involving the motor portion of the trigeminal nerve or much more rarely it may be a part of a multiple neuritis This neuritis may be due to any one of the numerous causes which can affect the peripheral nerves Peripheral disturbances of the motor portion of the trigeminal nerve may also follow inflammation of the portio minor between its origin in the brain stem and its distribution to the muscles of mastication On account of its close relation to the mandibular division lesions often involve this division of the nerve also The motor nerve may be compressed by neoplasms arising from the brain stem the neighboring cranial nerve the meninges or the skull by aneurysms of the vessels at the base of the skull thrombosis of the sinuses osteomyelitis of the cranial bones or injured by penetrating wounds fractures of the base of the skull etc The existence of a unilateral peripheral paralysis may be demonstrated by the loss of voluntary contraction of the masticatory muscles by the relaxed condition of the mylohyoid and digastric muscles in the floor of the mouth on the affected side and by the deviation of the jaw toward the paralyzed side and by the inability to move the jaw toward the unaffected side The jaw jerk is lost muscle atrophy and the reaction of degeneration appear after the acute phase is passed Unilateral paralysis disturbs but little the movements of mastication

Bilateral involvement of the peripheral nerves supplying the muscles of mastication may be the result of any one of the factors mentioned above if it affects the nerves bilaterally The result is a complete paralysis of the lower jaw which hangs open

Central —Unilateral or bilateral paralysis of the masticatory apparatus may follow nuclear involvement by acute or subacute inflammatory processes such as nonspecific or epidemic encephalitis polioencephalitis ascending paralysis progressive nuclear amyotrophy or chronic tuberculous or syphilitic conditions Neoplasms of the brain stem may involve the masticatory nuclei unilaterally or bilaterally In bilateral nuclear lesions the jaw falls and all movements are abolished The jaw jerk is lost atrophy takes place in the muscles and there is a reaction of degeneration in the muscles

artery, arteriovenous aneurysm or thrombosis of the cavernous sinus and by neo plasms which arise in the hypophysis

Segmental Disturbances —Disturbances in sensation corresponding to the segmental distribution of the trigeminal nerve are much less common than those of the peripheral type They depend upon intra axial disease and may result from vascular lesions such as hemorrhage thrombosis, or embolism from neoplasms in the medulla oblongata and the pons Varolii from conditions such as syringobulbia and multiple sclerosis and from inflammations such as epidemic en cephalitis In these types of disease, if the lesion progresses from below upward the disturbances will first affect the most aboral segments and gradually extend to the more circumoral dermatomes

Dissociative Disturbances —Pathologic processes within the neuraxis particularly syringobulbia may dissociate the various types of sensibility mediated by the fifth nerve Lesions which involve the descending root of the fifth nerve affect the pain and temperature fibers especially whereas lesions in the caput of the nucleus of the trigeminal nerve disturb the more discriminative types of sensibility It is possible also to involve separately the secondary fibers entering the spinal or medullary fillets the former carrying pain and temperature sensations the latter the discriminative sensibilities

Central Disturbances —The ability to lo calize points stimulated in the area supplied by the trigeminal nerve to distinguish the distance separating two simultaneously made contacts and the ability to recognize the character of objects touching the surface may be lost due to central lesions while the primary sense qualities are retained Conversely the ability to appreciate deep pressure and to localize stimulating points may survive a loss of superficial sensibility These deep types of sensation have been ascribed to the seventh cerebral nerve The course by which these stimuli reach the neuraxis is still unknown

Trophic Disturbances —Trophic changes in the mucous membrane the result of dis turbances in the trigeminal nerve may dis turb the sense of smell and also the sense of taste Trophic ulceration of the cornea may follow lesions or operative procedures on the ophthalmic division or the gasserian gang lion producing permanent opacity and dis turbance of vision Such trophic alterations favor the spreading of infection with result ing ophthalmia Interference with the glandular effector fibers of the fifth nerve may materially reduce and change the sal ivary and lacrimal secretions

Involvement of the cells of the gasserian ganglion by a virus may produce a *herpes zoster* in the distribution of any of the three divisions of the nerve This is characterized by burning and itching followed shortly by the development of groups of small vesicles on a reddened base which in time ulcerate It is usually associated with marked discom fort pain and tingling and is often followed by actual hypesthesia

Increased Sensibility (*Hyperesthesia*) —Pain may be produced and referred to the peripheral distribution of the nerve by lesions which irritate the root fibers The principal pathologic processes which produce such results are neoplasms inflammations and glioses Pressure of neoplasms originat ing from the brain stem the cerebellum or the cerebellopontile angle may irritate the nerve and produce pain which is referred to part or all of the trigeminal distribu tion

The most common condition characterized by pain in the trigeminal distribution is the so called *trigeminal* or *facial neuralgia* a full description of which will be found in the section on neuralgias page 1486

Trigeminal neuralgia may be associated with spasmodic reflex contraction of the muscles supplied by the seventh nerve It is then called *tic douloureux*

Perverted Sensibility (*Paresthesia*) — Irritative lesions of the peripheral branches or the central connections of the trigeminal nerve may sometimes pervert sensation and produce a feeling of tingling numbness or formication These symptoms are frequently produced by the irritation caused by gliosis either in the brain stem or thalamus and often prove to be the prodromal manifesta tions of hypesthesia and anesthesia

Hysteric Alterations in Sensibility — Hysteric disturbances are typically nonan atomic and do not follow any physiologic or morphologic laws in their manifestations *Hysteric hypesthesia* or *anesthesia* usually

sure neuritis Herpes zoster involving the geniculate ganglion may be sufficiently intense to involve the motor fibers of the facial nerve Blows by sharp or dull instruments resulting in direct injury or pressure may cause palsy of the nerve after its exit from the stylomastoid foramen Stab wounds and injuries from the application of obstetric forceps also act in this way Inflammatory processes in the parotid or face or mouth cavity often favor if they do not directly produce facial paralysis

Symptoms—The *paralysis* comes on rapidly in the course of a few hours without premonitory symptoms That due to local inflammation however may be preceded by the symptoms of the primary disease At times there is pain in the face or neck usually behind and below the ear for a short time before the paralysis appears and for a week or two afterward This has been attributed to a simultaneous involvement of the local sensory nerves (trigeminal cervical and occipital) Well marked paralysis affects all the muscles supplied by the facial nerve. The disturbance may be first noticed by friends on account of the distortion of the face or because of inability to whistle puff out the cheeks or close the eye The appearance of the face is characteristic The unaffected muscles draw the *mouth* toward the normal side and elevate its corner The wrinkles of the forehead and the nasolabial fold on the affected side are flattened out The eye is more widely open than the other and the lower lid slightly everted so that the mucous membrane is visible There is a slight deviation of the nose toward the sound side Voluntary movements—showing the teeth attempts to whistle closing the eyes—are possible only on the normal side and greatly increase the asymmetry As the lips cannot be tightly closed and the corner of the mouth droops on the paralyzed side saliva may escape from the corner of the mouth

The strength of the muscles may be tested in doubtful cases by attempting to open the tightly closed eyes or to draw back the corners of the pursed mouth by inserting the tips of the fingers into the mouth If the patient attempts to resist his own inflation of the cheeks the cheek of the paralyzed side is distended because of failure of the buccinator

The *eye* on the affected side cannot be closed nor the eyebrow elevated In attempts to close the eye the palpebral fissure remains open because of paralysis of the orbicularis palpebrarum the upper eyelid is lowered on account of relaxation of the levator palpebrae superioris and the eyeball turns upward until the cornea is hidden Since winking and the lid closure reflex are absent foreign bodies are apt to lodge on the cornea or conjunctiva and produce inflammation *Articulation* may be affected in that the labial sounds are defectively formed Relaxation of the lower lid allows the tears to escape on the cheek rather than through the lacrimal duct. Common sensation is not affected although taste may be imperfect or absent on the anterior two thirds of the same side of the tongue The secretion of saliva on the paralyzed side is usually diminished The hearing may be modified so that high notes are not accurately perceived while low notes are more readily heard than on the normal side

Herpes zoster of the auricle or external auditory canal is occasionally a symptom The electric excitability is normal at first but shortly response to faradic stimulation is lost and if the process be severe partial or complete reaction of degeneration develops during the first two weeks

Diagnosis—Fully developed facial palsy is recognized at a glance In order to discover the cause it is important to determine if possible the site of the nervous lesion whether it is in the tracts leading from the cerebral cortex to the facial nucleus in the facial nucleus itself or in the pathway from the nucleus to the periphery

Supranuclear lesions characteristically do not affect the superior facial branches which supply the orbicularis palpebrarum and the muscles of the forehead or involve them but slightly because they are innervated from both hemispheres neither do they alter the electric reaction nor the reflex excitability of the facial muscles they are frequently associated with hemiplegia of the same side rarely with that of the opposite side *Lesions of the nucleus or motor root* within the substance of the pons produce complete paralysis of the same side of the face but no disturbance of taste a change in the electric reactions loss of reflex excitability in the

Involvement of the trigeminal motor control may appear as the result of disease of the cerebral hemispheres These disturbances manifest the usual results of supranuclear lesions In pseudobulbar palsy there may be bilateral or unilateral involvement of the muscles of mastication Unilateral interference with these muscles makes difficult the approximation of the jaws on the side of the paralyzed muscles The lower jaw tends to deviate toward the side of the paralyzed muscles on account of the unopposed action of the unaffected pterygoid muscles The jaw cannot be protruded easily and there is lateral movement only toward the paralyzed side In bilateral disease the jaws cannot be approximated or protruded there is no atrophy and no reaction of degeneration if the lesion is supranuclear The jaw jerk usually is exaggerated

There may also be asymmetry of the soft palate the paralyzed side being somewhat lower because of involvement of the levator palati and azygos uvulae muscles

Progressive Facial Hemiatrophy—This condition was formerly attributed to nuclear trigeminal disease but it is more probable that the atrophy is due to an underlying involvement of the vegetative nervous system Since the fibers of the vegetative nervous system in this region are distributed by the small divisions of the trigeminal nerve trophic disturbances due to interference with the vegetative nervous system supply may correspond to the territories of the various branches of the trigeminal nerve The condition is characterized by a progressive atrophy of the bones cartilages and soft tissues of the involved portions of the face while the masticatory and facial muscles show no signs of the reaction of degeneration It is usually more intense in the middle and interior divisions Conditions which may cause it are injuries to the head and face infection exposure to cold erysipelas and osteitis of the jaw The atrophy results almost regularly after involvement of the cervical sympathetic ganglia The disease may be progressive for years or may come to a standstill at any stage in its development It does not seem to be definitely modified by any type of treatment

Henry Alsop Riley

Seventh to Twelfth Nerves

THE FACIAL NERVE

Paralysis—*Etiology*—Facial paralysis shows no special age or sex relationship although it but rarely occurs in childhood In some instances there seems to be a congenital origin *Facial palsy* may result from lesions situated anywhere from the cortical facial center in the lower rolandic region to the division of the nerve trunk in the parotid gland Lesions of the nerve trunk are the most frequent cause and produce so called peripheral or Bell s palsy

Supranuclear and *nuclear facial palsy* may result from tumors internal capsular hemorrhage, or thrombosis and encephalitic processes Congenital facial paralysis is usually bilateral and combined with partial or total oculomotor paralysis

Peripheral facial palsy may accompany gout diabetes mellitus tonsillitis puerperal infections and diphtheria The facial nerve may be affected in multiple neuritis especially in the alcoholic form and there is a type of syphilitic neuritis of the seventh nerve which occurs in the early stages of this disease Meningitis syphilis tuberculosis or suppurative processes may involve the nerve at the base of the skull Tumors of the acoustic nerve endotheliomata arising from the meninges and aneurysms and fractures of the base of the skull are other agents which may cause lesions of this part of the nerve In the fallopian canal it is involved by diseases of the middle ear and caries of the petrous portion of the temporal bone Fractures of the base of the skull may produce paralysis immediately after the interval of a few days because of inflammatory processes or later on account of the pressure of the callus Operations on the mastoid have at times directly injured the nerve By far the most frequent cause of facial paralysis is the neuritis accompanying exposure to cold or local chilling This may be brought about by application of ice to the side of the neck or face exposure to the draught from an open window or electric fan or washing the hair The exact mechanism of this process is unknown but the long course of the nerve through an unyielding bony canal in which there are a large number of lymphatics is believed to favor pres

Tumors of the trunk of the auditory nerve are more common than growth of any of the other cranial nerves Those occupying the cerebellopontine angle evoke symptoms which render diagnosis easy in many instances. The symptoms are those of internal hydrocephalus (headache vomiting and choked disks) and local manifestations such as impaired hearing and loss of function of the auditory nerve hemiasynergy cerebellar ataxia paresis of basilar cranial nerves especially the seventh sixth, fifth and possibly the ninth and tenth and nystagmus increased by looking toward the affected side

Diseases of the Vestibular Portion of the Auditory Nerve—*Meniere's Disease Acute Labyrinthitis*—Meniere's disease is an acute disturbance of the labyrinth due either to inflammation or to hemorrhage which is caused by various acute infectious diseases but especially by syphilis or arteriosclerosis *Entire destruction of the labyrinth* evokes *characteristic symptoms*—intense dizziness vomiting profound disturbance of equilibrium with a sensation of rotation of the body around its long axis and marked nystagmus The patient is not able to stand and lies upon the sound side. Turning on the back or other side causes intense vertigo These symptoms are pronounced for four or five days and then gradually subside but the nystagmus persists for a longer period and quick turning of the head may produce vertigo The disturbance of equilibrium eventually passes away but tinnitus and impaired hearing or deafness persist

Meniere's disease is a symptom-complex rather than a disease entity It is a labyrinthine imbalance and may be precipitated by a peripheral or central stimulus.

The peripheral stimulus is frequently a eustachian obstruction or an increased intracranial pressure Changes in the blood volume or in the vestibular fluid volume are presumably also causative factors

The causes of central stimuli are more vague and are believed to be similar to those causing neuralgia of the trigeminal nerve

The treatment of Meniere's syndrome is primarily directed to insure the patency of the eustachian tubes In the presence of general increased intracranial pressure or a local collection of fluid in the posterior fossa a spinal puncture will frequently be of value.

The researches of Fürstenberg Lashmet and Lathrop have led them to believe that Meniere's syndrome is due to a retention of sodium in the body These authors have outlined a treatment which has been found very beneficial in many instances of this disease Their treatment is as follows

1 Protein unrestricted or forced

2 Calories as indicated

3 Low salt content

4 Medication—Ammonium chloride, 3 Gm with each meal in capsules (6 capsules each containing 0.5 Gm taken during the meal), three days on and two days off The capsules should not be replaced by the enteric-coated pills because these sometimes pass through the gastro intestinal tract without being absorbed The ammonium chloride can be given in this dosage for an indefinite time without injurious effects

5 Water intake unrestricted although excessive *quantities of liquid should not be* taken

6 Vegetables and fruit daily except those listed below in groups A and B

7 Butter cream honey jellies jams sugar and candy permitted as desired

Foods to be Avoided

Group A all salt meats and fish or bread crackers and butter prepared with salt Carrots clams condensed milk raisins caviar cowpeas olives spinach cheese endive oysters

Foods to Be Taken no more than Twice Weekly

Group B lima beans beets buttermilk cantaloupe cauliflower celery chard dried cocoanut dried currants dates figs horse radish kohlrabi limes muskmelon peanuts, peaches mustard pumpkin radishes rutabagas strawberries turnips, turnip tops watercress.

Note all foods to be prepared and served without salt

Chronic labyrinthitis is usually secondary to disease of the middle ear Tinnitus and some degree of deafness usually precede the attacks of vertigo which vary in severity When severe enough to cause the patient to fall to the ground suddenly with a sensation that external objects are revolving about him they may be accompanied or followed by vomiting and nystagmus occurs

affected muscles and frequently *in addition* paralysis of the abducens nerve because of its close anatomic relationship with the pons

If the nerve is affected between its origin in the pons and the geniculate ganglion the symptoms are similar to those of nuclear origin except that the sixth nerve *is not* usually affected The eighth nerve *may* be involved Taste in the anterior portion of the tongue is normal Often the *secretion* of tears on the affected side is *diminished*

If the facial nerve *becomes involved* after leaving the stylomastoid *foramen*, complete paralysis of the *entire side* of the face ensues

The Nervus Intermedius of Wrisberg —The afferent fibers *of the nervus intermedius* convey *sensations* of taste through the glossopharyngeal *nucleus* to the brain, the *efferent* fibers join the submaxillary ganglion and *transmit* secretory impulses to the *submaxillary* and sublingual glands R Hunt *has* described instances of inflammation *of the* geniculate ganglion analogous *to* that of the posterior root ganglia in herpes *zoster* The *symptoms* of inflammation of the geniculate ganglion are the eruption of herpetic vesicles in the external auditory canal and pain in the auricle If the inflammation be so *severe as to implicate* the motor fibers of the facial nerve weakness of the facial muscles results and taste is lost over the *anterior* portion of the tongue When the auditory nerve is involved tinnitus, vertigo, diminution of hearing and possibly nausea and vomiting ensue

Hubert S Howe

AUDITORY NERVE

Paralysis —*Diseases of the Cochlear Portion of the Nerve* —Unilateral deafness *may* be produced by lesions of the temporal lobe Memory of words heard seems to be located in the *first temporal convolution* on the left side Very severe injuries to this area produce *word deafness* a condition of failure to understand spoken words although sounds are heard Injury of the auditory areas of both sides produces complete deafness Nuclear disease of the auditory nerve is practically unknown The termination of the nerve is often affected in labyrinthine disease The nerve trunk is frequently the seat of tumors and may be involved in tumors of the bone or meninges or by inflammation in the surrounding tissues Infiltration of the auditory *nerve* has been frequently observed in *leukemia* Toxic neuritis probably develops more frequently in the auditory than in any other cranial nerve It occurs in meningitis, *scarlatina*, and typhoid fever Implication of the auditory nerve is also found in tabes multiple sclerosis and other diseases Hemorrhages and inflammations may affect the labyrinths either one alone or both simultaneously This is especially *common in syphilis* but may take place in the *infectious* diseases (typhoid scarlatina mumps influenza, malaria and meningitis)

Diagnosis—Loss of function of the cochlear portion of the acoustic nerve impairs hearing As *disturbances of the middle ear* also produce the same effect nerve deafness must be distinguished from it by the reduction of hearing through bone conduction and defective perception of the higher notes on the scale The integrity of bone conduction is determined by Schwabach s *Rinne's* and Weber s tests

Schwabach s test is carried out by comparing the time during which a vibratory tuning fork is audible when applied to the mastoid process of the side affected with that on the normal side or of a normal individual In the impairment of hearing which accompanies a nerve lesion the period of audible bone conduction is shortened while in deafness referable to the middle ear this is normal or prolonged In performing the *Rinne test a vibrating tuning fork is placed* upon the mastoid process when the sound is no longer perceptible the fork is held opposite the external auditory meatus An individual with normal hearing then hears the sound again This is described as a positive result (positive Rinne) In diseases of the middle ear the sound conduction through the air is reduced and consequently the sound is not heard when the fork is opposite the ear (negative Rinne) In nerve deafness the test is positive as a rule unless there is a marked defect of hearing The *Weber test* is carried out by placing a vibrating tuning fork on the vertex of the skull In a normal individual the *sound is heard* with equal intensity in both ears If one ear is artificially occluded the sound is heard loudest in the ear in which the air conduction is thus interrupted This lateralization of sound occurs also on the side of the impaired hearing in individuals with diseases of the middle or external ear (sound conducting apparatus) This is referred *to as a* positive Weber sign A person with nerve deafness lateralizes the sound to the normal side ("negative Weber) The perception of the notes of the scale are tested by Galton s whistle Deafness for the higher notes of the scale is evidence of nerve deafness rather than of disease of the middle or outer ear

The symptoms of the various types of laryngeal palsy are most clearly indicated in Table 1 which is taken from Gowers

TABLE 1—LARYNGEAL PALSY

Symptoms	Signs	Lesion
No voice no cough stridor only on deep inspiration	Both cords moderately abducted and motionless	Total bilateral palsy
Voice low pitched and hoarse, no cough stridor absent or slight on deep breathing	One cord moderately abducted and motionless the other moving freely and even beyond the middle line in phonation	Total unilateral palsy
Voice little changed cough normal inspiration difficult and long with loud stridor	Both cords near together and during inspiration not separated but even drawn closer together	Total abductor palsy
Inconclusive little affection of voice or cough.	One cord near the middle line not moving during inspiration the other normal	Unilateral abductor palsy
No voice perfect cough no stridor or dyspnea	Cords normal in position and moving normally in respiration but not brought together on an attempt at phonation	Adductor palsy

In *complete bilateral recurrent laryngeal paralysis* the symptoms are complete aphonia lack of closure of the glottis in coughing and difficulty in breathing due not alone to insufficient width of the glottis but also to the fact that the vocal cords are drawn inward closer together on inspiration with consequent inspiratory stridor and severe dyspnea In some instances *central* or *peripheral injuries* of the vagus affect only the fibers of the recurrent laryngeal which supply only the posterior crico arytenoid muscles (abductors) This produces narrowing of the glottis to a mere fissure so that inspiration is stridulous while the voice is not seriously interfered with Isolated paralysis of the *superior laryngeal nerves* is very infrequent and is produced mainly by injuries or operations on the neck The diminished sensation which results in the pharynx and larynx causes a tendency to allow food to enter the larynx and paralysis of the cricothyroid muscles causes defective approximation of the cricoid and thyroid cartilages in phonation which results in hoarseness and lowering of the voice and rapid fatigue on intonation

HUBERT S HOWE.

THE SPINAL ACCESSORY NERVE

Paralysis—*Etiology*—The nuclei or roots of the spinal accessory nerve may be involved in the diseases of the upper cervical region of the cord (poliomyelitis progressive muscular atrophy, myelitis gliosis or tumor) The chief causes of peripheral paralysis are caries of the upper cervical vertebrae new growths meningitic exudations and lesions of the meninges or of the bone in the region of the jugular foramen In the neck the nerve may be injured by operations for the removal of cervical glands in the resection of cervical ribs by the pressure of tumors and rarely by primary inflammation of the nerve Lesions of the base of the skull also frequently affect the vagus and occasionally the hypoglossal

Symptoms—The symptoms of paralysis of the accessory portion of the eleventh nerve are entirely motor producing complete paralysis of the sternomastoid and incomplete paralysis of the trapezius Inaction of the sternomastoid is shown by inability to turn the head completely toward the opposite side In bilateral paralysis of the sternomastoid muscles the head tends to fall backward and in the horizontal position it cannot be raised forward without assistance Paralysis of the trapezius muscle is made manifest by an alteration of the outline of the neck and drooping of the shoulder The scapula on the paralyzed side is displaced downward and outward and rotated outward so that its inner border is inclined from below upward and outward instead of being parallel to the spine Elevation of the shoulder on the affected side is imperfect and the scapula cannot be actively approximated to the midline

HUBERT S HOWE

simultaneously, when less severe the patient reels but can prevent falling by grasping some stationary object The giddiness may persist for hours or pass off in a few minutes The attack is usually followed by nausea and headache, which last for some hours Between attacks there is some degree of deafness and tinnitus The symptoms may be unilateral or bilateral One ear is usually more severely affected than the other

The disease is not always progressive although the symptoms may recur from time to time for long periods

As a rule there is little difficulty in the diagnosis of this malady when the symptoms are severe but when the aural symptoms are not marked it may be confused with *petit mal* The absence of complete loss of consciousness and the presence of deafness and tinnitus however, suggest labyrinthitis rather than epilepsy

HUBERT S HOWE

THE GLOSSOPHARYNGEAL VAGUS AND ACCESSORY NERVES

Glossopharyngeal Paralysis—Isolated paralysis of the ninth nerve has not been observed for the nerve is so intimately associated with the spinal accessory and vagus that it is not affected alone Symptoms of glossopharyngeal palsy would include anesthesia of the upper portion of the pharynx loss of taste over the posterior third of the tongue *difficulty in swallowing and abolition* of the pharyngeal reflex

Vagus Paralysis—*Etiology*—The medullary nuclei may be involved in bulbar palsy medullary tumors syringomyelia epidemic encephalitis lues and multiple sclerosis The *intracranial portion* may be affected by growths or inflammatory processes in the meninges aneurysms diseases of the bones of the base of the skull and intracranial hemorrhages Operations on the neck may injure the vagus especially ligation of the carotid or the removal of glands or tumors The vagus is occasionally the seat of neuritis which has been attributed to the spine in such infectious diseases as typhoid pneumonia influenza and especially diphtheria Of the chemical poisons alcohol has the most important action on the vagus but lead and arsenic may also have some effect The *recurrent laryngeal branch* is especially prone to injury and is frequently damaged in removal of the thyroid or in ligation of the inferior thyroid artery It may be involved in atheroma or *aneurysms of the aorta* dilatation of the left auricle in mitral stenosis, tumors or enlarged glands of the mediastinum or neck and in tuberculosis and other affections of the lungs

Symptoms—Total vagus paralysis is seen most frequently in processes which involve the nerve trunk within the skull If one vagus alone be involved there is unilateral paralysis of the palate pharynx and larynx Frequently also there are evidences of involvement of other cranial nerves particularly of the glossopharyngeal the superior root of the spinal accessory, and the hypoglossal nerve The soft palate does not move *on the affected side and is* arched lower than on the normal side The voice assumes a nasal quality and the pharyngeal paralysis may produce a slight difficulty in swallowing There *is absence of the palatal and* pharyngeal reflex on the affected side The corresponding vocal cord is in the cadaveric position and does not move with either phonation or respiration *Disturbances of* cardiac rate or rhythm are not constant in unilateral vagus paralysis there may be slowing of the rate or alteration of the rhythm but these as a rule are not permanent Symptoms referable to the abdominal branches (*vomiting anorexia pains* etc) have been described but are too inconstant and unreliable to be of value in diagnosis

The most frequent and important symptom is *laryngeal paralysis* which may occur as the only result of lesions of the vagus itself or of the recurrent laryngeal In unilateral paralysis of the recurrent laryngeal the affected vocal cord is in the cadaveric position midway between abduction and adduction It does not move on either phonation or respiration During phonation which is carried out fairly well the healthy cord is moved across the midline and approximated to the paralyzed one There is some hoarseness but the quality of the voice is not greatly altered Respiration is not impeded except on very deep inspiration when there is some stridor

The symptoms of the various types of laryngeal palsy are most clearly indicated in Table I which is taken from Gowers

TABLE I—LARYNGEAL PALSY

Symptoms	Signs	Lesion
No voice no cough stridor only on deep inspiration	Both cords moderately abducted and motionless	Total bilateral palsy
Voice low pitched and hoarse no cough stridor absent or slight on deep breathing	One cord moderately abducted and motionless the other moving freely and even beyond the middle line in phonation	Total unilateral palsy
Voice little changed cough normal inspiration difficult and long with loud stridor	Both cords near together and during inspiration not separated but even drawn closer together	Total abductor palsy
Inconclusive little affection of voice or cough.	One cord near the middle line not moving during inspiration the other normal	Unilateral abductor palsy
No voice perfect cough no stridor or dyspnea	Cords normal in position and moving normally in respiration but not brought together on an attempt at phonation	Adductor palsy

In *complete bilateral recurrent laryngeal paralysis* the symptoms are complete aphonia lack of closure of the glottis in coughing and difficulty in breathing due not alone to insufficient width of the glottis but also to the fact that the vocal cords are drawn inward closer together on inspiration with consequent inspiratory stridor and severe dyspnea In some instances *central* or *peripheral injuries* of the vagus affect only the fibers of the recurrent laryngeal which supply only the posterior crico arytenoid muscles (abductors) This produces narrowing of the glottis to a mere fissure so that inspiration is stridulous while the voice is not seriously interfered with Isolated paralysis of the *superior laryngeal nerves* is very infrequent and is produced mainly by injuries or operations on the neck The diminished sensation which results in the pharynx and larynx causes a tendency to allow food to enter the larynx and paralysis of the cricothyroid muscles causes defective approximation of the cricoid and thyroid cartilages in phonation which results in hoarseness and lowering of the voice and rapid fatigue on intonation

HUBERT S HOWE.

THE SPINAL ACCESSORY NERVE

Paralysis.—*Etiology*—The nuclei or roots of the spinal accessory nerve may be involved in the diseases of the upper cervical region of the cord (poliomyelitis progressive muscular atrophy, myelitis gliosis or tumor) The chief causes of peripheral paralysis are caries of the upper cervical vertebrae new growths meningitic exudations and lesions of the meninges or of the bone in the region of the jugular foramen In the neck the nerve may be injured by operations for the removal of cervical glands in the resection of cervical ribs by the pressure of tumors and rarely by primary inflammation of the nerve Lesions of the base of the skull also frequently affect the vagus and occasionally the hypoglossal

Symptoms—The symptoms of paralysis of the accessory portion of the eleventh nerve are entirely motor producing complete paralysis of the sternomastoid and incomplete paralysis of the trapezius Inaction of the sternomastoid is shown by inability to turn the head completely toward the opposite side In bilateral paralysis of the sternomastoid muscles the head tends to fall backward and in the horizontal position it cannot be raised forward without assistance Paralysis of the trapezius muscle is made manifest by an alteration of the outline of the neck and drooping of the shoulder The scapula on the paralyzed side is displaced downward and outward and rotated outward so that its inner border is inclined from below upward and outward instead of being parallel to the spine Elevation of the shoulder on the affected side is imperfect and the scapula cannot be actively approximated to the midline

HUBERT S HOWE.

HYPOGLOSSAL NERVE

Paralysis of the tongue in cerebral disorders is a common result of lesions producing hemiplegia The nucleus is involved in bulbar palsy and in syringobulbia, and may be affected by tabes and diseases of the medulla oblongata As the hypoglossal nuclei are placed close together in the medulla both are involved, as a rule in medullary lesions, although instances of unilateral nuclear diseases have been recorded Paralysis of the hypoglossal caused by lesions of the nerve is produced mainly in the posterior cranial fossa (tumors of the brain or meninges basilar meningitis hemorrhages or *aneurysms of* the vertebral artery) The nerve may also be injured by fracture of the base of the skull and by various changes in the bone It is rarely injured outside of the skull, but may be severed by penetrating wounds or involved in deep abscesses or tumors or in dislocation or caries of the first cervical vertebra Cortical or supranuclear lesions produce paralysis of the opposite side of the tongue On protrusion the tongue deviates toward the paralyzed side because of the action of the unaffected genioglossus muscle and the inaction of the paralyzed one In supranuclear lesions there is no atrophy of the tongue Nuclear disease usually affects both nuclei but unequally The tongue cannot be protruded and atrophies so that fibrillary tremors develop in the wasting muscles The roots of the hypoglossal and pyramidal tracts for the opposite side of the body are involved rarely by a single lesion This produces a crossed paralysis of the tongue and limbs

Speech is not much affected by unilateral paralysis of the tongue but is much disturbed in bilateral paralysis as are swallowing and proper mastication

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DISEASES OF THE SPINAL NERVES

Hiccup —*Definition* —An intermittent clonic contraction of the *diaphragm often* associated with clonic contractions of the accessory muscles of *respiration*

The condition may occur at any age Sex plays no part It is due to a great variety of causes which irritate either the afferent pathway to the centers in the upper cervical part of the spinal cord the *centers themselves*, or their efferent pathway to the muscles

The afferent pathway may be irritated by swallowing very hot or irritating substances and by disorders of the esophagus or of the stomach such as gastritis and gastric dilatation Various intestinal disorders may initiate an attack, such as obstruction ileus strangulated hernia acute appendicitis acute pancreatitis and typhoid fever Peritonitis may be the cause Postoperative hiccup is *often very severe refractory to* treatment and so weakening as to endanger life The centers may be affected by tumors or meningomyelitis due to such infections as syphilis or epidemic encephalitis An epidemic variety of hiccup was reported in Paris in 1920 and also in New York A distinguished physician and his chauffeur were seriously ill within two weeks of each other In some cases no signs of epidemic encephalitis coexisted in these cases in others, the hiccup was a clonic part of that disease The attacks did not last over a week

Tumors and inflammatory disease of the mediastinum such as caseous glands enlargement of the heart and adherent pericardium are occasional causes

Uremia and alcoholism—acute or chronic —are toxic causes

Cancer metastases to the liver may be a cause

Finally the condition may be psychogenic in origin In these cases it often lasts for weeks but stops while the patient eats

Treatment —Pressure upon the phrenic

nerve between the heads of the sternocleido mastoids drinking cold water holding the breath or a sudden fright may be tried and will stop a mild attack Gastric lavage will often give relief when irritation of the gastric mucous membrane is present By hypo dermic 1/8 grain apomorphine or 1/100 grain *of hyoscine hydrobromate may be given* and repeated after three hours Morphine rarely succeeds Benzyl benzoate (1/2 drachm of a 20 per cent solution) sometimes stops an attack Inhalations of nitroglycerin or chloroform have been used Application of an ice bag to the neck ethyl chloride sprayed on the epigastrium repeated trac tion of the tongue pressure upon the eye balls mechanical dilatation of the esophagus by a small bougie and pressure upon the ribs near the origin of the diaphragm should all be tried in difficult and refractory cases

The treatment of hiccup by inhalational therapy of 5 to 10 per cent carbon dioxide in oxygen is of real importance in patients with pneumonia and in postoperative condi tions Inhalation of carbon dioxide should be pursued until the patient has had an absence of hiccup for a one minute period When it recurs as it often does inhalation of carbon dioxide should be begun again If no results are obtained with 5 per cent 10 per cent carbon dioxide in oxygen may be used It is at times necessary to give carbon dioxide until the patient becomes dizzy It must be recognized that long continued ad ministration of these high concentrations of CO_2 may cause unconsciousness and convul sions

Cervical rib is a developmental anomaly consisting of a more or less completely de veloped rib lying above the first thoracic rib and in relation to the seventh cervical vertebra

The various forms of cervical ribs may exist in two or more members of a family They usually do not produce symptoms or signs until the third decade Women are said to be more frequently affected than men

The *anatomic relations explain the dis* orders which these developmental anomalies cause The extra rib lies beneath the seventh and eighth cervical roots of the brachial plexus and in close relation to the subclavian artery

The ribs may be bilaterally symmetric or asymmetric but one side may produce a visible prominence They may very often be felt X ray examination establishes their presence Though ribs may be found on both sides but one side may produce symptoms

The relation of these various anomalies *to the subclavian artery and its branches is* of importance The extra rib either lies upon the first thoracic rib or upon the fibrous band of the cervical rib The transversalis colli or suprascapular artery may lie upon the cervical rib

The sympathetic system sends fibers from the first thoracic and inferior cervical gang lia to the plexus As the signs and symptoms indicate these may also be affected by pres sure of the extra rib or its fibrous continua tion

The cause of the appearance of signs and symptoms is sudden and severe or long lasting and oft repeated compression of the nerve roots as in carrying very heavy weights upon the shoulders continual irrita tion of the root by respiration the effort of childbirth and the drooping of the shoulder after adolescence Other causes such as periostitis have been described An unusual number of cervical rib cases appeared among troops in the B E F the pressure of rifles carried at the slope the straps of 90 pound packs or in gunners the carrying of heavy shells on the shoulder excited symp toms which would otherwise have never ap peared

Signs and Symptoms—These are motor sensory and vasomotor The motor manifes tations are weakness atrophy and various degrees of reaction of degeneration These are usually found in the muscles supplied by C 8 and D 1 but muscles supplied by the entire plexus may be affected Occasion ally after carrying heavy weights an iso lated paralysis of the serratus magnus mus cle may occur

The objective sensory changes may cor respond to the radicular limitations of the motor changes but more often they are *more limited in* extent or quite absent Sub jectively the patient has pain (neuralgia) or paresthesia or both in the forearm and hand

The vasomotor signs are cyanosis cold ness or edema due to pressure upon the

sympathetic fibers in the plexus These changes may become very severe and present the picture of early Raynaud's disease Paralysis of the cervical sympathetic (Dejerine Horner *syndrome*) *is occasionally* seen

There may be visible arterial pulsation due to pressure upward on the subclavian or one of its branches Thrombosis may occur in the artery distal to the rib The pulses may be unequal

Congenital syringomyelia is not infrequently associated with cervical ribs A developmental defect has occurred in both *the bony and nervous structures*

The *diagnosis* is best made by x ray examination though occasionally a fibrous *band alone may be present may not show* in the x ray film and may cause as serious *disorders as the bony ribs themselves*

The differential diagnosis from the various diseases causing pain paresthesia, weakness, muscle atrophy and vasomotor disorders is usually not difficult even without x ray examination Brachial neuralgia is not complicated by motor signs and symptoms The pain radiates from and through the shoulder as well as down the arm Brachial neuritis has a more widespread and uniform distribution of signs and symptoms Progressive muscular atrophy is not complicated by pain or other sensory disorders Syringomyelia presents a more difficult problem particularly when the vasomotor trophic disorders of this disease are mildly present The systematic examination of the reflexes throughout, and of sensation for the syringomyelic dissociation should make the differentiation simple Of course when both cervical ribs and syringomyelia are present the need for differentiation exacts most careful sensory examination and search for signs referable to tract changes in the spinal cord

Spinal cord tumors sufficiently large to cause the signs and symptoms of cervical rib produce other signs and symptoms Pain in cardiac disease such as that radiating down the left arm is unassociated with vaso*motor* and motor disorders

Treatment—Elevation of the shoulder and rest constitute the best initial treat*ment* Removal of the extra rib though a serious undertaking has resulted in cure or marked improvement in many cases The sensory disorders are often relieved at once The atrophy disappears much more slowly Massage and electric stimulation are indicated after operation Recently it has been shown that many cases can be cured by section of the scalene muscle without interference with the extra rib

Radiculitis—*Definition*—*An inflammation* of a spinal root

The spinal root on emerging from the *spinal cord is not fused into one structure*, but is divided into rootlets Each of these is covered by a layer of the arachnoid con*tinuous with the pia These cuffs* of endothelial cells extend outward to the point of fusion of the anterior and posterior roots *They thus form little* troughs in which infection can most easily find a resting place Outside of the arachnoid lies the dura which extends outward and is continuous with the perineural sheaths of the nerves The root may be defined as the emerging fibers from the point of their emergence from the spinal cord to the point of their fusion into the anterior and posterior roots

Etiology—Radiculitis is almost always dependent upon the occurrence of a meningitis and may therefore result from any of its causes Among these are syphilis tuberculosis acute coccal varieties and more rarely the exanthemata The symptomatology of *meningitis* is essentially that of *radiculitis plus signs and symptoms due to increased amount and pressure of spinal fluid* The symptomatology of meningitis usually given is in reality that of encephalomyelomeningitis a combination of the symptoms of infection of the brain and spinal cord and those of infection of the meninges Included in the latter are those of *radiculitis* Posterior spinal radiculitis is herpes zoster It is characterized by spinal root pain—often agonizing—which may last weeks months or ever after X ray to the affected spinal root area is very often dramatically curative It should be given at once Periapical abscess of a tooth may cause radiculitis *and allergic* reactions may give rise to fluctuating nerve root symptoms and signs A more frequent cause is trauma *to the spine caused by* extrusion of a nucleus pulposus on to a spinal root the slipped intervertebral disc may impinge on *both the spinal cord* and on one

or two spinal roots The ligamentum subflavum hypertrophied by injury or chronic infection from the gut or pelvis may produce the same symptoms and signs In Bellevue Neurological Service instances have occurred where two levels ' usually cervical and lumbar were easily demonstrated due to the simultaneous presence of two compressing slipped discs in the same person Not infrequently only radicular signs and symptoms are found Radicular syndromes dependent upon epidemic encephalitis, extramedullary tumors cancer metastases Pott s disease or other forms of spondylitis are not infrequent They are rarely simple but complicated by other signs and symptoms elsewhere in the body Tabes dorsalis at its onset is but a polyradiculitis The radicular signs and symptoms due to increased spinal fluid pressure in tumors of the brain are considered under that subject Telangiectasis may give rise to acute or fluctuating radicular cauda equina symptoms

The disease may be acute subacute or chronic

Symptoms.—The signs and symptoms of radiculitis are sensory reflex motor vasomotor trophic and glandular

(1) Sensory —The most striking and frequent sensory symptom is pain (neuralgia) It may be extremely severe and lancinating or dull and aching It occurs in the area of distribution of the roots involved It is often referred to as inside ' The points of emergence of the nerve trunks are not tender Pressure upon muscles does not increase the pain Coughing sneezing or yawning increases the pain by the increase in spinal fluid pressure. Movements which stretch the roots also increase the pain

Sensations of pins and needles formication heat and cold also occur in areas of root distribution

Objectively there are sensory losses of various kinds touch pain heat and cold always in a radicular distribution The entire root distribution may not be completely affected nor are the areas of several roots always completely affected Patchy involvement therefore results In oculomotor paralysis from syphilitic basal meningitis partial lesions due to involvement of some rootlets only are almost the rule

(2) The reflexes both deep and superficial are occasionally exaggerated at the onset Later they are diminished or absent Babinski s sign and other similar signs as well as clonus are usually absent The spinal cord is seldom affected

(3) Motor disorders are not so common as sensory disorders They consist of paresis or paralysis and atrophy of the muscles supplied by a root. The electric reactions may show various degrees of reaction of degeneration—rarely complete Simple diminution of reaction to faradic and galvanic current is frequent In lesions of the eighth cervical and first thoracic roots there may appear the syndrome of cervical sympathetic paralysis

(4) Trophic disorders occur in the chronic varieties. The skin may become more hairy or smoother Glossy skin may result The nails become rigid and curved There may be hyperostoses on the bones supplied by the affected roots Perforating ulcers may occur Cyanosis coldness paleness and various disorders of sweating may occur The spinal fluid changes are those of the cause. Slipped disc most often gives rise to increased spinal fluid protein *i.e* more than 45 mg

Diagnosis—The diagnosis is made by elimination of evidence of myositis on one hand and neuritis on the other In the first one finds tonic reflex spasm of muscle local muscular tenderness no sensory changes normal reflexes and no chemical alteration of the spinal fluid In neuritis there is nearly always local muscular weakness local reflex change and motor and sensory signs of the neural type There is no evidence of increase of pain by root stretching or by increased spinal fluid pressure from coughing yawning and sneezing

Prognosis and Treatment—The prognosis depends entirely on the effectiveness of the treatment of the primary cause For slipped disc surgical intervention may be necessary X ray therapy should be used for the pain of herpes zoster Massive intramuscular injections of thiamine chloride (100 or 200 mg daily or on alternate days) for two months or more in all forms of radiculitis is good treatment whatever else be done The pain of diabetic neuritis is often the result of diabetic radiculitis—treat the diabetes cor

rectly use thiamine as described and give all necessary analgesic drugs—phenacetin aspirin, and even codeine Paravertebral injections of alcohol have become popular and, one notices are often done previous to correct diagnosis Remember never do anything to a patient you would not have done to your self for the same ailment Remember, too that these injections are in the realm of 'blind surgery 80 per cent alcohol is potent and its employer must be both expert and optimistic. Paravertebral injection of saline solution is not hurtful and may be used both diagnostically, to determine further therapeutic action, and as treatment in its own right The writer has cured many cases of severe sciatic pain by injecting 200 cc of saline through the sacrococcygeal joint, a procedure which may be repeated two or three times

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PARALYSIS AGITANS

(Shaking Palsy Parkinson s Disease)

Definition—Paralysis agitans is a slowly progressive organic affection of the central nervous system beginning in the fifth or sixth decade of life and resulting in a characteristic rhythmical tremor of resting muscles, associated with stiffness and slowness of movement It was first described by James Parkinson in 1817 and is one of the classical forms of disorder of executive nervous function with preservation of the pyramidal tract and lower motor neurons hence called *extrapyramidal disease* Conditions exhibiting the same type of rigidity with or without the same type of resting tremor are termed Parkinsonism

Etiology—The specific cause is entirely unknown Since the disease occurs in later life there is commonly associated arteriosclerosis, but the characteristic disorder and pathology are independent of this Arteriosclerosis may result in a similar but not identical clinical condition Trauma may shortly precede the first symptoms The onset is more commonly precipitated by an emotional crisis or physical exhaustion, and there is no reason to believe that the precipitant effect of trauma is other than through the effect of these factors in drawing attention to the previously unnoticed insidious onset. It is remarkable that focal vascular lesions tumors and all variety of experimental lesions in animals fail to produce the characteristic syndrome which must therefore require a very selective type of damage to nervous structure

The incidence is slightly higher in men than in women and is not limited to any particular race or continent or any type of occupation So called 'juvenile forms" are open to strong suspicion of being the result of epidemic encephalitis The occurrence of more than one case in one family is an extreme rarity

Morbid Anatomy—The nervous system presents no change that is obvious to the naked eye except that on the cut surface through the midbrain the dark pigmentation of the substantia nigra is less striking than usual Only careful histologic study will reveal a loss of many of the cells of the substantia nigra and a similar outfall of the larger cells of the globus pallidus the remainder being pale, some shrunken There is no evidence of inflammation or of vascular change and no constant lesion has been found in any other part of the nervous system or in the muscles

In the closely related postencephalitic parkinsonism the loss of cells in the substantia nigra is more complete the changes elsewhere less definite and small foci of round celled infiltration may be present Some however (Tretiakoff, Cobb and Benda) consider the two conditions identical The evidence for a distinct juvenile pallidal form (Hunt) is slender

Symptoms—The tremor or slowness of movement and set facial expression are commonly not noticed by the patient until his attention is drawn to them by others so slow and insidious is the onset. Any one of these symptoms may be the first to ap

pear soon followed by the others Most commonly the rhythmical tremor of the fingers of one or the other hand is first noticed as the limb rests after some excitement or exertion In weeks or months the tremor becomes more constantly present whenever the limb is at rest The patient now becomes aware of a general slowing and loss of freedom of movement The lower limb on the affected side drags if he attempts to run The tremor and slowness gradually appear in the other limbs. He begins to feel a difficulty in writing in dressing himself in maintaining balance in turning around quickly or in rising from a chair all gradually resulting in great disability Once confined to bed the patient slowly develops greater rigidity and owing to limitation of coughing is liable to terminal bronchopneumonia

There is no disorder of sensation The relative immobilization of joints usually results in arthritic changes The shoulder joints in particular may become painfully limited In the earlier stages awkward postures may be long maintained without apparent difficulty but later the difficulty in turning may result in great discomfort in bed.

The sphincters are not affected nor is swallowing or digestion The mind remains clear The occurrence of confusion is usually the effect of drugs used in treatment Speech becomes slurred and indistinct only in later stages when movements of the tongue jaw and larynx are slowed and incomplete At this stage in paralysis agitans food is incompletely chewed and saliva tends to collect in the mouth and drool over the lips

Bouts of reactive nervous depression and anxiety are common During these the symptoms are more prominent lessening again with return of mental calm Sudden exacerbation of symptoms should thus indicate the transient effect of anxiety and not an extension in the organic pathology

Physical Signs —The general appearance of the patient is so characteristic that to the practised eye it is alone sufficient to establish the diagnosis beyond doubt All manifestations of the disease can be traced to two abnormalities tremor and rigidity

Parkinsonian Tremor—This is a fairly regular rhythmical alternating contraction of opposing muscular groups at the rate of 2 to 5 a second It is best seen in the fingers and thumb which beat against each other as if rolling a pellet (pill rolling) There is irregular fluctuation in the amplitude of the movement, so that from time to time it lessens in the fingers and appears instead at the wrist, or elbow then again in the fingers In the limbs it is most prominent in distal joints The same rhythm actuates the ankle or knee with similar gentle fluctuation It can be seen in the lips during momentary relaxation or in the eyelids when lightly closed (blepharoclonus) or in the relaxed tongue or palate It rarely actuates the trunk musculature or extra-ocular muscles

Parkinsonian tremor is seen at rest or in relative relaxation It is damped by movement or strong contraction and reappears only after an interval thus differing radically from the behavior of intention cerebellar or hysterical tremor When severe in degree it may occur in sleep

Parkinsonian Rigidity—In the affected limbs all muscles at each joint offer a soft plastic resistance to passive or active movement This has no sudden give as has spasticity and is usually a little more intense in the flexors than in the extensors resulting in a continued slightly flexed posture of the limbs In early stages it is most easily felt by gently extending and flexing the patient s fingers or wrist Commonly rhythmical fluctuations in the relaxing resistance are felt (cogwheel phenomenon) corresponding to the beats of the tremor When no tremor is present the cogwheel relaxation indicates its imminence The rigidity is more widespread than the tremor and its affection of the spine and neck results in the stooped posture with slightly flexed upper limb and hip joints that is an obvious feature of the fully developed disease Only in very late stages is the rigidity intense

Power of muscular contraction is retained to the end and can be tested by the patient s ability to resist a passive opposing movement Voluntary movement nevertheless becomes slow and weak owing to the rigidity Thus paralysis refers only to impairment of movement not of power of contraction of muscles The *reflexes* are accordingly not altered though the tendon jerks may be submerged by the rigidity that is

already activating the muscles The plantar responses remain flexor

Parkinsonian rigidity affects the facial musculature, slowing expression and impairing or abolishing the smaller natural movements and spontaneous blinking This unnatural stillness combined with increased tone in the levators of the eyelids gives rise to the staring *'parkinsonian mask'* As in the limbs, the rigidity may at first be one-sided, and is likely to be mistaken for facial weakness until a full voluntary effort or more violent emotion show slower but nevertheless full power of contraction on the affected side The eyelids once tightly closed are slow to open, and similar slowness of movement and tremulous relaxation is seen in the tongue Small steps in walking, also due to limitation of movement and slowness in compensatory movement give rise to difficulty in maintaining balance, especially in turning where a few rapid steps backward (retropulsion') may occur In his hurried steps (festination) the patient may literally chase his center of gravity The struggle against rigidity is apparent in all types of movement and many small movements virtually disappear This may occur at a *stage when rigidity is very slight* so that absence of swinging of an affected arm may be a confirmatory sign when there is doubt about the presence of palpable rigidity

There is no change in sensation or in the special senses. The cerebrospinal fluid is unaltered in pressure or contents

Diagnosis —The fully developed syndrome of paralysis agitans is unmistakable In early stages of development however it must be differentiated from *multiple sclerosis* where the tremor is of intention or cerebellar type and thus increased by movement, and usually accompanied by nystagmus and where any stiffness in muscles is in the nature of spasticity with reflex changes *Hysteria* may also be manifested by rhythmical tremor which however tends to be localized, not affecting the lips and tongue for instance and increased by attempted use of the part

There is a form of fine rhythmic tremor of the outstretched fingers lessened during movement which is a family characteristic ('familial tremor") This appears in the second or third decade and then remains constant A similar tremor (*senile tremor*) may appear in the hands in the fifth or sixth decade This is increased by movement and sometimes associated with a tremor of the head Both these tremors lack the postural changes and rigidity of parkinsonism and follow a benign course

More difficulty attaches to clear differentiation from *other varieties of parkinsonism* *Postencephalitic parkinsonism* (see Epidemic Encephalitis, p 63) has the same type of tremor and rigidity, the same facies and slowness in movement but differs in its onset at any age from childhood upwards its tendency to become arrested and even remit after some months, and its usual association with defect in convergence of the eyes and in reaction of the pupils to accommodation Even when these criteria are lacking the rigidity is greater and the tremor slightly faster and more intense than the gentle undulation of true paralysis agitans Because of this greater intensity of ridigity the postencephalitic has usually greater difficulty in speech, in disposing of salivary flow, and frequently suffers from attacks of spasmodic deviation of the eyes (oculogyric crises) and spasmodic torticollis, or torsion *spasms of the trunk* The original acute stage of encephalitis is frequently unrecognized or forgotten, and the absence of such history is therefore not a useful criterion

Arteriosclerosis is not uncommonly the cause of parkinsonism in elderly subjects The tremor is lacking however and the fixed expression slowness in movement, and gait in short steps are the sole representatives of the syndrome Disturbances in the sphincters and progressive memory disorder are commonly associated due to the damage to the basal ganglia being part only of a general cerebrovascular degenerative process

Syphilitic parkinsonism is seen in the rare occurrence of the characteristic tremor in a tabetic (Wilson and Cobb) It is possibly only a coincidental relationship of the two disorders

Progressive lenticular degeneration (hepato lenticular degeneration Wilson s disease) is an extremely rare familial disease which also exhibits slowly progressive tremor and rigidity The onset is in adolescence with a regular fine tremor of the hands mild rigidity of parkinsonian type and a very

characteristic slowing of expression and vacuous smile A golden pigmentation of the outer edge of the cornea is pathognomonic Cirrhosis of the liver is present but ascertained only at autopsy

Slowness in movement and fixed expression may result from damage to the basal ganglia as part of generalized cerebral disease such as general paresis myoclonic epilepsy or resulting from very severe intoxications by manganese or carbon monoxide but are not sufficiently distinct to merit consideration as separate clinical entities

Prognosis —The course of paralysis agitans is so slowly progressive that the patient may continue to live as long as twenty years and may succeed in carrying on an occupation especially of intellectual kind for several years after the onset The total duration depends largely upon nursing care after the first five years

Postencephalitic parkinsonism runs a variable course some cases showing steady progression to a bedridden state in five to ten years In most the course is arrested at some stage and the patient adjusts himself to his disability for many years A very few mild cases have recovered or changed in type

Treatment —The treatment is essentially symptomatic No known form of therapy will alter the course of the disease Much can be done in adjusting the patient s life to his disability and in view of the deleterious effects of stress anxiety and fatigue there should be careful planning to avoid these Within the limits of fatigue regular exercise is beneficial Regular passive movements and very light massage lessen stiffness and discomfort Electrical treatment is seldom helpful and often increases rigidity

Where anxiety and depression are present simple *psychotherapy* can often achieve remarkable improvement As in other kinds of chronic disease optimism and bright surroundings greatly assist the patient to make the most of his reduced capacity

The effect of any therapy is difficult to assess owing to the strong suggestive effects of any new treatment in these patients The solanaceous (hyoscine stramonium hyocyamine atropine) group of drugs has a remarkable effect in lessening the rigidity without however materially altering the tremor To secure this effect the drug has to be given in full dosage large enough to cause its physiologic side effects—dryness of the mouth and impairment of accommodation of vision The most generally useful is *stramonium* then *hyoscine* and it is considered best to change from one to the other every six months Some physicians (see Vollmer) consider that better results are obtained by combinations of these drugs There is a wide individual variation in tolerance Pilocarpine gr $\frac{1}{10}$ may be added to the morning dose if dryness of the mouth is a complaint and spectacles fitted to allow accommodation Very many patients have taken such dosage for years without ill effect After the age of fifty drugs of this group are less well tolerated and toxic confusion delirium insomnia or restlessness are likely to result In true paralysis agitans therefore a simple sedative tonic with phenobarbital at night usually is more satisfactory

Attempts to abolish the tremor by various *surgical procedures* have been made The induction of spasticity by cortical or high spinal operation abolishes the tremor but only when in such degree that it is of itself a disability

D DENNY BROWN

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ACUTE CHOREA

(*St Vitus Dance Sydenham's Chorea*)

Definition —Acute chorea is an acute *infectious disease characterized by involuntary*, coarse muscular twitchings psychic changes and a propensity to endocarditis and polyarthritis It was first described by Thomas Sydenham in 1686 It is usually seen in children but in rare instances occurs in adults It is commoner in cities than in the country

Etiology —A nonhemolytic *Streptococcus* is generally believed to be its exciting agent Toxins from this organism or some unascertained source act upon the brain, particularly its basal ganglia to produce the characteristic *symptom complex of a non* epidemic encephalitis *Fright* or *trauma* may precipitate or exaggerate an attack and *emotional shock* seems to play a noteworthy role in the production of relapses when a *locus minoris resistentiae* has been established In children *mimicking* may produce a habit spasm but not true chorea

Age —In the decade between five and fifteen *years of age the susceptibility* to acute chorea is greatest Rarely the disease is seen in infants or even at birth but 80 per cent of all cases occur during childhood Adults are rarely affected except during pregnancy The senile type of chorea is usually a symptom of some other organic disease of the brain

Sex —Girls are about two and one half *times as susceptible as boys*

Season —The highest incidence occurs during the months from December to April

Heredity —A certain vulnerability to the disease expressed in a type of constitution may be heritable The Negro race and full blooded American Indians seem relatively immune

Pregnancy predisposes to acute chorea and *favors a relapse in previously choreic* individuals The younger primiparae are most liable

Acute Infections —Various acute infectious diseases (particularly measles and scarlet fever) may modify and coincide with acute chorea although they play no directly causative role

Rheumatism per se is not really a cause of chorea it is rather part of a multiple symptom complex (rheumatism, endocarditis, chorea) In the series of choreics reported by Jones and Bland 72 per cent showed some evidence of rheumatic fever rheumatic heart disease complicating 54 per cent (40 per cent, in Hedley s report) The actual causative agent is possibly a streptococcus which is responsible for the rheumatism endocarditis or chorea *alone or to* gether Teeth tonsils and paranasal sinuses are suspected as portals of entry

Morbid Anatomy —The lesion is a low grade *meningo encephalitis* with at least some striatal (caudate?) localization The involuntary movements are presumed to be attempts by the cerebral cortex to compensate for failure of subcortical mechanisms

Cerebral *congestion common to all acute* infectious processes is found *Hyperemia* and *thromboses* may be more or less uniformly scattered through the brain and meninges Small nodules occur in connection with the vessels particularly in the gray matter of the cortex and basal ganglia Freeman stresses the absence of those exudative and destructive changes in the locus niger *which are typical of epidemic encephalitis*

The electroencephalogram shows generalized abnormalities dysrhythmias that are nonspecific among encephalopathies decrease in alpha rhythms and presence of continuous slow wave activity of increased amplitude (Usher and Jasper)

The cerebrospinal fluid may be normal or show a mild pleocytosis increased tension *and glucose content and diminished* calcium Eosinophils tend to be increased in the blood The sedimentation rate may be raised The serum calcium is lowered Warner found 9 66 mg per cent, compared with 10 14 after recovery

Symptoms —The *onset* of the disease may be gradual or comparatively rapid It is frequently accompanied by insomnia headache anorexia and constipation and occasionally by vomiting Fever is usually of low grade or absent. The severity of the disease varies greatly

There are three *cardinal symptoms* spontaneous *movements ataxias* and weakness to which may well be added a fourth psychic changes The patient typically makes involuntary but conscious muscular jerks and twitches He cannot coordinate

movements normally and is unable to hold a muscle or muscle group in steady contraction he tends to overreach the mark (dysmetria) in pointing tests and suffers some loss of muscular power Generally these signs vary in degree on the two sides of the body There is also a noticeable psychic alteration frequently dulled perception and diminished attention occasionally a tendency to hypomania.

The typical *twitching movements* are rather quick and of moderately wide excursion Each begins suddenly and passes rapidly and often resembles a gesticulation or grimace They are not rhythmic one or several movements in one direction are followed by movements in the opposite direction but no two are of the same extent The rapidity of choreic movement is greater than that of athetosis and less than that of a tic The movements generally cease during sleep but not in severe cases In the most severe conditions they entirely prevent sleep Sensory stimuli may increase them It is common during the examination when the disturbance is mild for choreic movements to be absent at first later when the novelty of the procedure wears off and the patient s attention lessens the involuntary activities gradually appear as though breaking through inhibition

Ataxia of the extremities produces a stumbling gait Dysmetria and asynergia appear in attempts to perform complicated acts such as piano playing Hypotonia is generally well marked being evidenced by signs like the choreic posture of the hand (flexion at the wrist and hyperextension at the metacarpophalangeal joints) The inability to maintain a tonic muscular contraction is quite typical and is readily demonstrated by the hand grip which will relax suddenly and involuntarily

Weakness may be evidence of disturbance in the pyramidal tract The other motor signs can be referred to lesions in the extra-pyramidal basal ganglial and cerebellar systems Very marked weakness produces the paralytic type of chorea and not the common spasmodic type Varying degrees of involvement of different systems explain the dissimilar symptom-complexes In each individual the symptoms remain fairly constant in type throughout the course of the disease Extrapyramidal signs are characteristic of chorea, but pyramidal signs apparently do occur Extension of the great toe (Babinski sign) is far less common than flexion the deep reflexes are characteristically diminished but occasionally increased Dana describes a *tonic reflex* evoked by tapping the patellar tendon the foot flies up and remains up unusually long or a second reinforcing jerk occurs In most cases the tendon reflexes and muscle tone differ appreciably on opposite sides of the body

Acute chorea can affect any number of muscles or muscle groups Beginning usually in the hands and arms symptoms spread to the face and later to the legs Facial muscles alone may be involved or the tongue continue choreic jerking after other muscles function normally Motor disturbances are commonly unequal on opposite sides and a pure hemichorea may occur

Speech is involved in about 25 per cent of patients The abnormality is not a paralysis but a disorder of articulation It may amount to hesitancy incoherence or even transitory mutism

The *pupils* are often dilated although they react normally as a rule Oppenheim mentions hippus as a symptom. There are no trophic changes nor endocrine sequelae The electric excitability of nerves and muscles is normal or slightly increased The sensory findings are negative except that occasionally there are pains and tenderness in the limbs

Most choreic patients suffer *psychic alterations* of some degree Before the typical motor signs appear the disposition frequently becomes irritable later the dulness inattention carelessness and loss of memory may be so pronounced as to suggest mental deficiency Mild emotional disturbances are usual and violent hysteric outbursts occasional. In the rarer severe conditions exhaustive psychoses (*chorea insaniens*) may develop with mild movements great mental excitement delirium visual hallucinations and delusions Pregnant women are especially prone to the more serious mental complications

Special attention should be given the heart, joints and nasopharynx In a *sinusitis pharyngitis tonsillitis* or *dental caries* foci of infection are often found *Articular in*

flammation usually precedes the chorea *Cardiac complications* on the other hand are more likely to appear after it is established or during its involution tachycardia whether functional or organic commonly occurs simultaneously

Duration and Termination —The duration of acute chorea formerly reckoned at from one to six months has been shortened to a quarter or one fifth that length by the use of fever therapy It is not yet certain whether this treatment will reduce the frequency of recurrences Hitherto these have followed 15 to 50 per cent of initial attacks

Disappearance of symptoms is gradual Personality changes, such as neurasthenic or schizoid traits may tend to persist Very exceptionally acute chorea becomes chronic or is succeeded by a tic

Outside of pregnancy a fatal termination is rare (1 2 per cent) and due most often to cardiac complications It may ensue without them in a maniacal state (*chorea gravis*) Willson and Preece report a mortality in the chorea of pregnancy varying from 19 per cent for cases without previous history of chorea or rheumatism down to 6 8 per cent for those with a history of both

Diagnosis —Sydenham's acute chorea is a disease entity to be differentiated from choreas dependent on conditions unrelated to rheumatism The following diseases may present some diagnostic difficulty

Hysteria protean in its manifestations may readily simulate chorea The history of the disease and general appearance of the patient the lack of organic signs should suggest hysteria This condition is more common at puberty begins more suddenly evokes more purposeful and more closely localized rhythmic movements is interrupted by intervals free from movements and is usually associated with anesthesia and analgesia

Tic or *habit spasm,* is still more localized abrupt, momentary contractions affect single muscles or groups of physiogically related muscles Such movements are coordinated and purposeful and remain the same in repetition Choreic movements are more like aimless wiggling vary constantly and affect different muscles Tic is more subject to the will

Choreic and choreo athetoid twitchings are occasional sequelae of attacks of *epidemic encephalitis* Differentiation of chorea from encephalitis demands familiarity with the latter s changing peculiarities in different epidemics It has no rheumatic or cardiac association its transient and migratory pareses and its epidemic character should be of value in making the differential diagnosis

Severely paretic examples of Sydenham s chorea can readily be confused with *acute anterior poliomyelitis* especially during an epidemic of the latter Choreic movements if detected make the diagnosis

Rarely is *senile chorea* a Sydenham s Most cases are related to such gross organic lesions of the brain as occur in posthemiplegic chorea and Huntington s chorea The movements of chorea are less active in senility than in childhood

Posthemiplegic hemichorea may be confined to an arm or leg and depends on the cerebral process that gave rise to the hemiplegia *Little s disease* cerebral hemiplegia or diplegia may be associated with some choreiform movements Its appearance at or shortly after birth is evidence that the condition is not Sydenham s chorea and its typical spasticity and pronounced pyramidal tract signs are characteristic *Congenital athetosis* is marked by similarly distinguishing cerebral signs Each individual movement of athetosis begins and develops more slowly than in chorea

Huntington s chorea can be distinguished by the heredity the past history the onset in late adult life the chronicity the greater breadth of movements and the dementia

Paramyoclonus multiplex is practically always bilateral and is seen in the sudden contraction of a single muscle or muscle bundle with fibrillary twitching Muscles are not involved in groups The face so generally affected in Sydenham s chorea practically always escapes

Friedreich s ataxia occasionally suggests chorea by producing abrupt movements in the face and extremities The gait is however more staggering and reeling and the subsequent course makes the diagnosis certain

Dystonia musculorum deformans in its early stages has been confused with chorea The twitching is more athetoid and the

pathognomonic torsion spasm as well as the evolution differentiates it

Various *intoxications* and *multiple sclerosis* with rhythmic tremblings are in rare instances confused with chorea

Treatment.—Several weeks rest in bed benefits most cases and is quite essential for the more severe Rest is aimed particularly at reduction of sensory stimulation Application of a cold pack once or twice daily or a warm bath at night for the milder cases is recommended Phenobarbital 0 016 to 0 1 Gm., may be given several times daily for a few weeks in mild cases Chloral hydrate 0.5 to 1 Gm with sodium bromide in equal or greater amount can be given by mouth (or rectally with starch) occasionally over a shorter period Sodium amytal 0 4 to 0.8 Gm. by mouth or rectum can be used for relief of great motor restlessness excitement and insomnia Hyoscine hydrobromide in 0 4 to 0 6 mg doses is valuable for subcutaneous administration in severe conditions Morphine and even chloroform inhalations may be needed to control intense paroxysms.

Repeated lumbar punctures with moderate drainage apparently prove beneficial during the rest treatment especially when the disease is severe

Salicylates given to tolerance are sometimes valuable Calcium and parathyroid may be useful Nirvanol (phenyl-ethyl hydantoin) is unsafe The classic treatment of chorea with Fowler s solution of arsenic is largely outmoded and probably useless Sulfanilamide has given some good results but further experimenting with other sulfonamides is needed Favorable effects of thiamine niacine pyridoxine and others also need further study

Fever therapy has proved successful Sutton and Dodge give a triple typhoid vaccine containing 1000 million typhoid and 750 million each of paratyphoid A and B per cubic centimeter intravenously The initial dose is 0 05 or 0 1 cc followed by increasing doses once or twice daily with occasional resting days until all choreic signs disappear A febrile reaction of 104° to 106° F is sought and the vaccine doses are run up to around 5 cc Subacute carditis does not contraindicate fever therapy Fever induced mechanically by the Kettering hypertherm short wave diathermy etc is equally satisfactory From about 5 to 20 heatings are given each of two and a half hours duration at 105° to 106° F

Carious teeth and infected tonsils which constitute especially dangerous foci of infection should be carefully examined and treated Particular attention is due the heart which is often the seat of endocarditis Dilatation is a common abnormality Direct therapy is necessary for whatever cardiac complications are present

In convalescence anemia and malnutrition can be combated by administration of cod liver oil with malt iron and arsenic tonics Ample food should be given somewhat more stimulating in character than the simple milk and vegetable regime suitable to the acuter stages Massage and passive movements are often beneficial Electricity should be avoided In a survey of pediatric after-care Irving found that supervised activity did not lengthen the course of the disease and that choreic convalescence was not hindered by association with other patients Outdoor exercise work and play rather favored complete return to good health

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SPASM TIC AND TORTICOLLIS

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SPASM TIC AND TORTICOLLIS

A *spasm* is a sudden involuntary rigid contraction due to muscular action When persistent it is called tonic when characterized by alternate contraction and relaxation clonic Spasm is usually attended by pain

It interferes with function and produces involuntary movements as well as distortion

The type known as *reflex spasm* is evoked by some exciting stimulus such as a local lesion in the skeletal motor, or sensory domain

A tic is a recurrent spasmodic involuntary muscular action confined to a few muscles or muscle groups without the presence of a peripheral irritative cause Presumably a tic is cortical in origin.

Pain, often present with reflex spasms and even a symptom of certain tics is the particular feature of the so-called *tic douloureux* which is, properly speaking not a tic It is a special type of reflex spasm of the face associated with paroxysmal facial pain of great intensity and dependent upon changes in the corresponding fifth cranial nerve A reflex spasm may persist after the excitant is relieved This is often true in blepharospasm which is a clonic tonic spasm of the orbicularis palpebrarum muscle usually beginning in some period of ocular irritation but persisting as a habit after its subsidence

Local hysteric spasms have no physical excitant but are evoked by a psychic stimulus Like a tic in this regard they are separated from tic only somewhat arbitrarily They are less constant in localization than a tic and are chiefly recognizable by the fact that they vary greatly in extent and degree in the same patient from time to time and are associated with hysterically emotional even convulsive states Disappearance of a spasm during sleep is not a sign that it is necessarily hysteric Reflex spasms and other organic spasms may be absent then also Persistence of the spasm during sleep however, is sure evidence that the condition is organic in nature and not hysteric

A so called *habit spasm* is a persistently repeated involuntary clonic motion which when sufficiently severe is a tic A very common type is the ordinary facial tic which produces a frown a sidewise twitch of the mouth or similar movement.

A tic is radically different from the movement in chorea since in the latter condition no one movement is repeated regularly again and again Tics while often psychogenic have in individual cases an accompanying physical reflex element In such instances the boundary lines between these types of spasms all but disappear It is conspicuous that tics occur in patients prone to psychasthenic reaction, and that those sometimes associated with acute psychasthenia are transient Such tics can best be ignored in therapy, for they disappear when the psychasthenia is treated

A type of spasm which is being more and more widely recognized depends on lesions in the midbrain and basal ganglia It can be labeled *central spasm* Unusual states of clonus with clonic or tonic movements must all be studied with such changes in mind The prevalence of encephalitis has made this clear In individual cases it is necessary to look for other signs of previous encephalitis, or to consider whether infection or trauma of any kind has altered the integrity of these basic centers of motor control

Torticollis is a tonic or tonic clonic spasm of the neck muscles which causes wryneck. It is usually considered a distinct disease but is, more correctly one of the types of spasm just described The torticollis which accompanies cervical Pott s disease is a reflex spasm which is increased in later stages by the mechanical misalignment Another reflex torticollis is the so called "labyrinthine" type This follows irritation of the semicircular canals on one side At times torticollis is a habit phenomenon, really an example of tic Still other types are central in origin, that is, they follow organic changes in the region of the basal ganglia

Treatment—The treatment appropriate for torticollis and for all other local spasms depends entirely on their etiology It varies therefore from the cure of tuberculous spondylitis to the removal of psychic abnormalities Spasm of central origin may be helped by midbrain sedatives such as hyoscine Torticollis may occasionally be improved by surgical division of the spinal accessory nerve or by division of the combined trunks of the three upper cervical segments

THOMAS K DAVIS.

DYSTONIA MUSCULORUM

(*Tortipelvis*)

Dystonia as a general term indicates a state of abnormal tonus of muscle but *dystonia musculorum* describes a clinical en

ity It is a rare chronic disease characterized by irregular, involuntary, clonic contortions of the trunk and proximal muscles of the extremities and characterized as well by constantly shifting tonus in the affected muscles The face is usually not involved

The disease affects both sexes and usually begins near the end of the first decade of life It results from certain progressive lesions in the lenticular nucleus. While it is possible to conclude that the changes are degenerative their exact cause is not yet clear

While the patient is sitting quietly or lying down the symptoms are almost entirely in abeyance but they begin as soon as voluntary movements are initiated The abnormality is most conspicuous in walking and the contortions bend the body and twist it forward and sideways in a most bizarre manner They seem focused at the pelvis

The muscles remain free from trophic changes The normal reflexes persist abnormal responses referable to lesions of the pyramidal tract are absent and sensation is unimpaired The mentality remains normal

No therapy has produced important or lasting benefit

THOMAS K. DAVIS

THE CONVULSIVE STATES

A convulsive reaction is a phenomenon common to all animals possessed of an integrated neuromuscular system Given an adequate stimulus—say the injection of a convulsant drug—every animal will have a convulsion However the amount of stimulus required varies for different species of animals and among men for different individuals Two conditions underlie the phenomenon of convulsions first a constitutional tendency towards this reaction and second an appropriate stimulus Probably in each person subject to seizures both of these conditions are present The proportion of the two varies from person to person and every degree of gradation exists but for practical purposes clinical convulsive states may be divided into two groups first those in which an inborn hereditary tendency seems the predominant though not the exclusive factor These may be called *genetic* (essential or idiopathic) *seizures* In the second group some post conceptual environmental condition seems the predominant though not the exclusive factor These may be called *acquired* (symptomatic) *seizures* They include jacksonian, traumatic and organic epilepsy tetany, eclampsia and syncope

WILLIAM G LENNOX

EPILEPSY

The most important (and most feared) of the convulsive states is epilepsy

Definition—The word means seizure Defined clinically the syndrome consists of recurrent paroxysms of (1) impairment of consciousness or of other psychic functions (2) involuntary muscle movement and (3) disturbance of the autonomic nervous system These recurring symptoms are concurrent with a dysrhythmic discharge of the neuronal cells of the brain recordable by means of the electroencephalograph Defined physiologically epilepsy is a symptomatic paroxysmal cerebral dysrhythmia

Incidence—Epilepsy occurs in about 0.5 per cent of the population or in approximately 600 000 persons in the United States The onset of seizures is predominantly in early childhood and in adolescence yet about 30 per cent of private and clinic patients begin to have seizures after the age of twenty Males and females are equally affected though the onset of seizures is earlier in females than in males due possibly to a greater hereditary factor The number of children in the family or their order of birth is not influential Statistics for judging the relative frequency of seizures among racial and economic groups are inadequate

Etiology—Of the two main causes of epilepsy the genetic and the acquired the former is the most important Of patients who are subject to seizures approximately three fourths give no history or on examination present no evidence of significant brain or bodily injury Among the near relatives of unselected epileptics both epilepsy and cerebral dysrhythmia occur approximately five times more frequently than in the general population Among identical twins only one of which has epilepsy and evidence of brain injury the normal twin nevertheless possesses an hereditary dys

rhythmia of brain waves In a given patient the relative importance of this genetic factor is greater if evidence of brain injury is lacking if there is a family history of epilepsy or migraine and most important of all if one or both parents have cortical dysrhythmia on electroencephalographic examination The practical aspects of genetics will be discussed under Prevention The acquired (symptomatic) causes of epilepsy are multiple, although evidence of such a cause is found in less than one fourth of patients A genetic factor must play a part in acquired epilepsy for these patients have three times as many relatives with epilepsy as persons in the general population Following are the disorders in which seizures occur more frequently than in the general population

1 Congenital defects of the central nervous system cerebral aplasia cerebromacular degeneration congenital mental defect, and tuberous sclerosis

2 Pathologic changes in the brain developing after birth the various types of encephalitis and of meningitis multiple sclerosis general paresis cerebral abscess, toxoplasmosis parasitic cysts tumors hemorrhage, trauma, gliosis scars porencephalic cyst chronic arachnoiditis, arteriosclerosis and senile degeneration

3 General conditions or diseases uremia toxemia of pregnancy, alcoholic intoxication cerebral edema, pernicious anemia polycythemia hemorrhage asphyxia carbon monoxide poisoning oxygen intoxication, protein shock anaphylaxis Raynaud s disease acute fever in children angioneurotic edema Stokes Adams syndrome orthostatic hypotension syncope carotid sinus reflex migraine craniofacial hemiatrophy tetany, insulin or electric shock, hyperventilation and hysteria

4 Convulsant drugs cocaine strychnine magnesium sulfate picrotoxin absinthe thujone camphor, caffeine ergot nicotine lead epinephrine and sulfathiazole

The incidence of epilepsy in these disease conditions varies widely but except for convulsant drugs and brain tumor does not exceed 10 or 15 per cent This is about the proportion of persons in the population who have some degree of cortical dysrhythmia Whether those who develop seizures are recruited from among those who had a pre existing dysrhythmia awaits investigation Diabetes and schizophrenia are the only conditions with a reported negative correlation with epilepsy

In a group of nearly 2000 clinic and private patients whose records were tabulated by Lennox the following conditions were believed to be the principal cause of seizures brain trauma 5 7 per cent, congenital defect or birth injury, 5 6 per cent brain infections 4 2 per cent, brain tumor 2 6 per cent cerebral circulatory defect 1 9 per cent, extracerebral causes 0 9 per cent In 77 6 per cent of the patients the principal cause of seizures could not be demonstrated although if electroencephalographic examinations had been possible almost all of these would have displayed a cerebral dysrhythmia

Morbid Anatomy—Since the time of Hippocrates physicians have recognized that the brain is the seat of epilepsy and have searched for characteristic pathologic changes—but in vain At autopsy neuropathology is often encountered even when unsuspected in life Atrophies gliosis arachnoiditis are most common but morbid changes when found seem to be either a result of seizures or an acquired condition which is but a contributory factor in seizures The morbid anatomy if any of the sixty acquired causes mentioned under Etiology will be found in other sections of the volume The book by Penfield and Erickson deals especially with the important subjects of trauma and tumors

Pathologic Physiology and Chemistry—The underlying phenomenon of genetic (essential) epilepsy is a dysrhythmia of the electrical potentials of the brain which is a hereditary trait and which is the resultant of chemicophysical peculiarities of the discharging cells of the brain Structural abnormalities of the brain either genetic or acquired seem to be only contributory Seizure discharges arise from live functioning neurones and not from dead neurones the supporting structures of the brain or from foreign bodies embedded in it Pursued to its lair the peculiar chemistry of epilepsy is the chemical structure of the gene which comes to be expressed in the chemical structure or the chemical reaction of the neuronal cells of the brain This pathochemistry in

turn finds expression in the rate and voltage of the electrical pulsations of the brain Before grappling with the chemistry of epilepsy we may first summarize its electrophysiology The following condensed statement is culled from the writings of Dr and Mrs Gibbs and Lennox

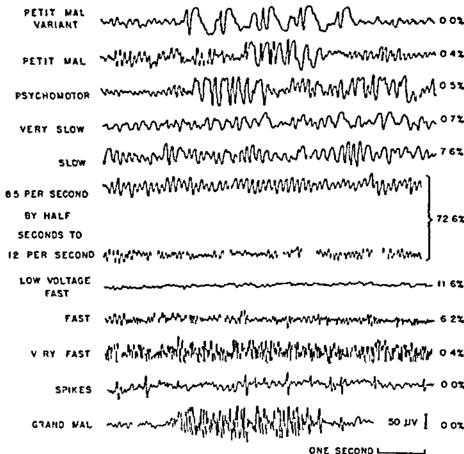


Fig 193—Classification of electroencephalograms used by the Gibbs The upper three and the bottom two tracings contain "seizure discharges" These together with very fast or very slow rhythms are classed as definitely abnormal Tracings moderately slow or fast are classed as slightly abnormal Others including low voltage fast tracings are termed normal Tracings showing dominant frequencies of 9 9½ 10 10½ 11 and 11½ per second are omitted The figures at the right of each tracing indicate the percentage of 1 000 adult controls who were classed as having that type of record In the lower right hand corner is the deflection made by a current of 50 microvolts and the time occupied by one second Tracings are reduced 2½ times

The Electroencephalograph—Proof of Hughlings Jackson s definition of epilepsy as a sudden excessive and unruly discharge of neuronal cells had to await the patient labor of Hans Berger who in 1929 published the first electroencephalograms

During the epileptic seizure the patient s electrical potentials increase greatly in amplitude and become either faster or slower The three main types of seizures are distinguished by different wave patterns fast in *grand mal* slow in psychomotor seizures and alternately fast and slow in *petit mal* The last named the three a second alternate dart and dome formation is distinctive perhaps pathognomonic for *petit mal* The electrical perturbations which accompany seizures may like the seizures themselves be a mixture of two different patterns In the period between seizures approximately 90 per cent of epileptic patients display disturbances of brain waves which may be called asymptomatic dysrhythmia Samples

of these various wave patterns are shown in Fig 193 a condensation of the Gibbs classification of electroencephalograms The various abnormalities occurred more often in the epileptics than in the controls as follows paroxysmal discharges of high voltage fast slow, or alternately fast and slow waves (seizure discharges)—34 times more often, a dominant frequency which was either very slow or very fast—19 times more often and a frequency which was only slightly slow or fast—twice as often Eighty six per cent of patients with *petit mal* 36 per cent of those with psychomotor seizures and 2 per cent of those with *grand mal* display in their routine electroencephalographic record the pattern of seizure discharge which corresponds with their clinical seizures In a given patient the degree of dysrhythmia varies greatly from time to time but is usually at a maximum as a convulsive seizure approaches Although ordinarily widespread over the cortex dysrhythmia may be most pronounced or even confined to one area, such a focus indicating the site of a cortical lesion The degree of abnormality varies spontaneously but is also influenced by brain activity and by alterations in the chemistry of the body Mental concentration sensory stimulations opening or closing the eyes sleep variations in the pH carbon dioxide oxygen sugar and other elements of the blood alter the frequency of abnormal as well as of normal waves However the different types of dysrhythmia may not all be affected alike The alternate dart and dome dysrhythmia of petit mal is most easily influenced by an altered chemical environment Severity of symptoms and of the cortical dysrhythmia do not necessarily run parallel Indeed 2 per cent of the normal control group and 10 per cent of the normal adult relatives of epileptics had grossly abnormal records

Abnormal brain waves may be inherited or acquired The pattern of the electroencephalogram is an hereditary trait and in the great majority of patients their cerebral dysrhythmia is a transmitted and not an acquired condition a conclusion supported by the experience with twins which was mentioned under Etiology Decision as to whether a given dysrhythmia is transmitted or acquired calls for electroencephalograms of parents or other near relatives and a search for evidence of acquired pathology or metabolic disturbance of the brain Obviously, the use of the electroencephalograph is of great potential value in tracing the transmission of epilepsy and in the detection of individuals who may be predisposed Because dysrhythmia is encountered in an unusual proportion of certain nonepileptic groups such as criminals behavior problem children and psychotic persons the local war against seizures may become a general war against cerebral dysrhythmia without regard to what the associated dysfunction of mind or of action may be

The Chemicophysiology of Epilepsy—As previously stated a disturbance of the electrophysicochemical make up or reaction of the neuronal cell and its antecedent gene underlies the disordered electrical pulsations of epilepsy Detection of molecular abnormalities in these submicroscopic fragments of the body is beyond present means of examination Indirect information can be gained from analysis of body fluids the value of the observations being in inverse proportion to the distance of the fluids from the brain

Analysis of the blood entering and leaving the brain at the same time that the functional electrical activity is being recorded provides the most direct information yet available about the metabolism of brain cells which are discharging abnormally Using this method of study Lennox Gibbs and Gibbs have observed that the carbon dioxide of both the arterial and the internal jugular blood tends to be unusually high in patients subject to *grand mal* and unusually low in those subject to *petit mal* Alterations in the carbon dioxide tension and in the pH of blood passing through the brain have a profound effect on the abnormal electrical activity of the brain *petit mal* activity being accentuated by low and *grand mal* by high tensions of carbon dioxide Perhaps most intriguing is the observation that the brains of patients subject to *petit mal* tend to have a lower respiratory quotient and to consume less glucose per unit of oxygen consumed than normal individuals Spiegal has reported a parallel relationship between various procedures which promote convulsions and an increased permeability of the brain tissue of

animals The ratio of potassium within the nerve cell to that of sodium without is influential in nervous discharge and is related to the activity of the adrenal cortex and to the sympathetic nervous system and the emotions McQuarrie and his associates speculated that the increased urinary excretion of potassium which they observed at the time of seizures might represent leakage of potassium from cells of the brain

The reviews by Lennox and Cobb and by Goldstein and MacFarland demonstrate the many efforts which have been made to find significant abnormalities by laboratory procedures Epileptics tend to have low basal metabolic rates slow startle responses and a slow peripheral blood flow but on the whole the findings of these many studies have been negative or only coincidental Most observers agree however that the physiology of epileptics like their brain waves seems to be unstable with unduly great hour to hour or day to day fluctuations

More rewarding has been the study of conditions which tend to produce or prevent seizures in persons already subject to them These observations do not ferret out the etiology of seizures but they demonstrate methods of altering the seizure threshold and thus contribute to the therapy of epilepsy Various conditions influence seizures especially *petit mal* 1 Acidosis induced by starvation a ketogenic diet ingestion of acids or acid forming salts breathing air containing a high concentration of carbon dioxide and the formation of excess lactic acid through vigorous muscular work tend to inhibit seizures Alkalosis induced by overventilation or by ingestion of alkali tends to precipitate seizures 2 Dehydration as shown by Temple Fay tends to inhibit seizures and water intoxication has long been recognized as a convulsant McQuarrie observed that the convulsant effect of water drinking was accentuated by the simultaneous injection of pitressin but that convulsions did not result if a saline solution replaced the water 3 An increased tension of oxygen or hyperglycemia tends to prevent seizures and anoxemia or hypoglycemia tends to induce them 4 Various drugs tend to inhibit seizures and others to cause them The mechanism of their action has been little studied The anticonvulsant action of dilantin deserves especial attention because this drug has little or no hypnotic effect it causes hirsutism and hyperplasia of the gums and its value seems to be greatest in certain types of seizures

Symptoms —The symptoms which were mentioned under Definition may occur in varying proportions in different patients and in the same patients at different times A seizure may be a transient impairment of consciousness so slight as to be unrecognizable or a convulsion of demoniacal fury

Aura —About one half of patients experience premonitory symptoms of a seizure These are various consisting perhaps of a sensation of dizziness or of discomfort in the abdomen or in patients having a localized cortical lesion a numbness or spasm of an extremity The aura which corresponds to the first gust before a storm may be too brief to permit the patient to sit or lie down

Grand Mal —The outstanding phenomenon is excessive tonic and clonic activity The patient loses consciousness his muscles become rigid respiration is suspended and if not supported he falls Because of the apnea his face becomes livid and the veins engorged As the cyanosis deepens the pupils dilate and become insensitive to light normal reflexes are abolished blood pressure rises perspiration and saliva flow The asphyxia and accumulation of carbon dioxide in the blood presumably sets reverse forces in action and after less than a minute the rigid tonic contractions are replaced by shock like clonic jerks air enters the lungs and frothy saliva possibly mixed with blood is blown from the lips by the oxygen starved lungs The patient s body bathed in ill smelling perspiration then lies limp and exhausted A convulsion if severe is followed by heavy sleep and by headache vomiting muscular soreness and depression of spirits Convulsive attacks occur at variable intervals some patients having only one or two a year others many a day Eight per cent of patients have experienced *status epilepticus* a condition in which one convulsion succeeds another with no intervening periods of consciousness

In general convulsive movements which are one sided or localized are more common

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A nearly pure type of acquired epilepsy is the variety called jacksonian named after Hughlings Jackson the English neurologist In this type convulsive movements or abnormal sensations begin in the small muscles of the hand foot or face and slowly spread the patient being a helpless witness The 'march' may end spontaneously or be arrested by squeezing the part or it may spread to the rest of the body and loss of consciousness and a generalized convulsion ensue The area of the cortex which corresponds to the portion of the body first involved is called the 'trigger zone

Petit Mal—Loss or impairment of consciousness is the predominant symptom This comes without warning starts and stops abruptly lasts but a few seconds and is without after symptoms Usually there are rhythmic motions of eyelids or of the head at the rate of three a second synchronous with the spike of the EEG This form of seizure occurs usually in genetic epilepsy and is most common in females and during adolescence It is the form most frequently recurring the most innocuous and yet the most resistant to drug therapy The term pykno epilepsy is sometimes used

Psychic Equivalent Seizures—These are variously spoken of as psychic psychic variants or psychomotor seizures Amnesia is the predominant symptom The person is out of contact with his environment but activity is not suspended He may perform purposeful acts but is not subject to command and after the period of confusion is over has no recollection of what took place and may not know that a seizure has occurred The seizures are longer than *petit mal* lasting from a few seconds to minutes or hours The patient may make chewing motions and his body may rotate or become slightly rigid but muscular movements if present are tonic and not clonic as in *petit mal* In prolonged episodes the patient may act as though intoxicated and may become violent especially if restraint is attempted Psychomotor attacks are more frequent in men than in women and in adults than in children

Borderland Phenomena—The portion of the brain involved in a seizure discharge determines the display of symptoms which follows Some seizures are bizarre indeed such as running fits vasovagal attacks in which there may be only pallor nausea, or other visceral phenomena sleep attacks or narcolepsy, and migraine headaches which are sometimes spoken of as sensory epilepsy

Diagnosis—The real problem in the diagnosis of epilepsy is the detection and separation of the genetic from the half hundred acquired causes of seizures The accumulation of evidence must precede this sifting process

A clear description of the seizure when obtainable usually gives a clue as to whether the seizure is hysterical tetanic syncopal jacksonian or if epileptic like whether it is *grand mal petit mal* or psychomotor

The patient's *family history* is to be searched for instances of convulsions spasms faints fits spells dizziness, lapses of consciousness migraine feeblemindedness or psychosis The patient should be asked about the circumstances of his birth any head injury which resulted in unconsciousness infections such as meningitis encephalitis whooping cough or pneumonia and symptoms such as enuresis sleep-walking night terorrs unexplained faintings dreamy periods and headaches The use of alcohol with the time relationship if any, to seizures and the function of the gastrointestinal tract and relationship of constipation to seizures should be determined With women patients one must know the menstrual history and the relationship of seizures to menstruation and pregnancy There must be a detailed account of seizures and of previous examinations and treatments

The survey of the patient should include first a *general physical examination* with particular attention to the posture the general physique and the circulatory system The neurologic examination should be painstaking and include inspection of the eye grounds and mapping of the visual fields Detection of an early brain tumor requires a keen eye for small signs Following is the proportion of certain signs encountered in a group of 1500 clinic and private patients

definite nystagmus, 2.5 per cent lefthandedness 7 1 per cent, some peculiarity of speech, 22.8 per cent reduced coordination of movements 4.3 per cent, paralysis of an extremity, 0 6 per cent, and a positive Babinski sign 5 6 per cent

Of *laboratory examinations* much the most important is the electroencephalogram A tracing which shows outbursts of high voltage fast slow, or alternately fast and slow waves is almost certain evidence either *of epilepsy or of a strong predisposition to it, and weighs heavily against a diagnosis of* hysteria Routine examinations should include urine and blood roentgen ray films of the skull and if a lesion of the brain is suspected lumbar puncture with note of spinal fluid pressure concentration of protein number of cells and the Wassermann and gold sol reactions A pneumoencephalogram and sometimes exploratory operation is needed if other evidence suggests a localized brain lesion In suggestive cases other tests such as measurement of the basal metabolism the blood sugar curve or Roentgen rays of the digestive tract, may be indicated Determination of the intelligence quotient and of traits of personality are often necessary for proper treatment Usually careful search will discover not one but several causes and sometimes more than one disorder such as a hybrid *form of epilepsy and hysteria* of epilepsy and migraine or of tetany and epilepsy

Prognosis —The many factors involved *in epilepsy and the lack of statistical evi*dence from noninstitutional patients prevents accurate forecasting Doubts about the future refer to length of life relief from seizures maintenance of mentality and of social usefulness

Life expectancy is somewhat reduced for most patients because of the chances of external injury from unexpected loss of consciousness or of internal injury from frequently repeated and severe convulsions The brain injuries of acquired epilepsy if not operable bring additional dangers Prognosis regarding seizures is more hopeful if the patient has not suffered brain injury if cortical dysrhythmia is not too severe if mentality is normal if seizures began late are infrequent or of the *petit mal* type if intelligence and finances permit adequate treatment and if seizures are controlled by drug therapy Fortunately, increasing age seems to exert a healing influence

Mental Deterioration —Impaired mentality when it occurs is the most distressing aspect of epilepsy Fortunately contrary to common lay and medical opinion serious deterioration is unusual Of 1905 private and clinic patients examined 67 per cent were found to be mentally normal 23 per cent slightly deteriorated and 10 per cent *definitely deteriorated* Of 1638 *patients who were mentally normal at birth* 75 *per* cent were normal when seen by the examining neurologist and only 7 per cent definitely deteriorated The proportion of mentally normal was 54 per cent in patients with a history of brain injury The proportion of mentally normal decreases somewhat with the passage of years and with the total number of attacks suffered Yet of patients who had been afflicted twenty five years or longer 46 per cent were mentally normal Psychomotor seizures *grand mal* and *petit mal* are harmful in the order named Mental deterioration when present may be due to one or more of the following causes heredity brain damage suffered prior to the onset of seizures the effect of the seizures themselves or of the underlying brain dysrhythmia over medication and psychologic traumas Pa*tients may show unpleasant traits such as* egotism rigidity, moodiness perseveration elements in the so-called epileptic personality Such traits are rare in mentally nor*mal patients who have received intelligent* treatment Whether the life of the epileptic can be happy and useful depends largely on his social and psychological background and treatment

Prevention.—Eugenics is the principal prophylaxis against genetic epilepsy Sensibly to reduce epilepsy in succeeding generations eugenics would need to be applied not only to persons subject to genetic seizures but also to the much larger number of normal persons with hereditary cerebral dysrhythmia especially of the seizure discharge' type Approximately half of the near relatives of epileptic patients have disturbed brain rhythms and in about 90 per cent of patients one or both parents have some degree of dysrhythmia If an epileptic, or a normal person who has cortical dys

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obedience to instructions the daily measured output of urine should not exceed the volume of fluid allowed not counting that contained in solid food Patients experience chronic thirst so that in spite of its simplicity, the procedure is not popular

Ketosis or dehydration should be continued only if trial demonstrates an actual reduction in the number or severity of seizures Patients with frequent severe seizures or with definite underlying cerebral pathology *are least likely to be helped*

Anticonvulsant Drugs—Three drugs are of proved usefulness bromides phenobarbital and phenytoin sodium This is the order of their discovery and the inverse order of their effectiveness in controlling seizures Ten to 20 grains (0 6 to 1.2 Gm) of sodium or potassium bromide are given three times a day usually in a watery solution Long-continued and heavy medication may result in an acneform eruption or in somnolence and *mental sluggishness* The chloride intake should be kept steady since that ion if excessive may displace the bromide. For accurate treatment the bromide content of the blood should be measured Phenobarbital, at an increased price is sold also under the trade name of luminal The daily dose for adults is from 1½ to 3 grains (0 1 to 0 2 Gm) although double this amount may be taken The occasional patient with an idiosyncrasy for the drug will *have a diffuse macular rash within a few* days after beginning its use The amount which can be taken is usually limited by somnolence Soluble phenobarbital is used for intravenous injection

Phenytoin Sodium—Putnam and Merritt in 1938 first demonstrated in patients the anticonvulsant action of sodium diphenyl hydantoinate The official name is phenytoin sodium the trade name in America is dilantin sodium The original claims of the Boston workers have been confirmed and phenytoin sodium is recognized as the drug of choice for the majority of patients suffering from seizures both because of its *relative effectiveness and its lack of hypnotic* effect However its administration requires vigilance and experience It is most effective for the psychomotor type of seizures for which other drugs are of little use and relatively ineffective for petit mal The effective dose may approximate the dose at which side effects appear Therefore the physician beginning with 1½ grains (0 1 Gm) three times a day for adults and one-*half* that amount for children *will gradually* increase the amount until seizures are controlled or toxic symptoms appear The maximum amount which adults can tolerate is 9 grains (0 6 Gm) a day Most prominent of the toxic symptoms are incoordination (shown by tremor nystagmus or instability *of movements*) *gastric discomfort or cutaneous* rash Some patients especially children have annoying hyperplasia of the gums Symptoms rarely encountered are hirsutism loss of weight fatigue excessive activity or psychotic manifestations Some of these symptoms are inconsequential others call for a reduction in the dose or even abandonment of this form of therapy Obviously this is a medicine to be avoided by concerns which treat patients by mail *and by the physician who is unable or unwilling* to learn by reading and experience. If phenytoin sodium is not fully effective, phenobarbital may be added the full dose of phenytoin being continued Many patients discouraged by the defeatist attitude of the profession have turned to mail order concerns The basis for these epilepsy 'cures is phenobarbital or bromides The cost of phenobarbital purchased in this way is nearly ten times the cost of that bought *at a drugstore*

Care During Convulsions—During a convulsion the principal effort is to avoid injury Some soft substance should be inserted between the teeth to prevent biting of the tongue and clothing about the neck should be loosened Efforts to cut short the attack are useless After the convulsion is over the patient should be allowed to sleep or remain quiet until he feels normal again. In the presence of *status epilepticus* soluble phenobarbital *may be given parenterally* in 3 to 5 grain (0 2 to 0.3 Gm) doses, repeated after twelve hours if necessary Oversedation with its prolonged hang-over effect is however to be avoided A shorter acting drug is paraldehyde one to three drachms (4 to 12 cc) given parenterally When other means fail and exhausting convulsions threaten life resort may be had to etherization A cleansing enema can do no

rhythmia marries he should choose a person whose brain waves are normal thereby greatly reducing the existing chance (about one in forty) that each child will be epileptic In advising about marriage, the physician must remember that the patient and his spouse may have desirable genetic traits which may outweigh his tendency to seizures Furthermore like many other conditions epilepsy *per se* is not inherited, but only the predisposition If precipitating acquired factors can be avoided the predisposition may lie dormant

Public responsibility for the prevention of acquired epilepsy concerns the reduction of infectious diseases which involve the brain brain injuries which result from traffic or industrial accidents and war Individual prophylaxis involves the avoidance of asphyxia or injury at birth later brain trauma or emotional upsets There is also the possibility of treating dysrhythmia before seizures begin especially if a history of infantile convulsions or other suspicious symptoms are present

Treatment *Remedial*—Since the causes of seizures are multiple treatment must be individual and many sided The intelligent and interested family physician who has the confidence of the patient is in the best position to carry out a rounded program the steps of which are (1) correction of observed abnormalities, (2) raising the seizure threshold and (3) the maintenance of mental health and social usefulness

Correction of Abnormalities—The repair of encephalopathies requires the services of a skilled neuro surgeon The most hopeful situations are superficially located or encapsulated tumors or localized cortical scars Penfield reports worthwhile reduction of seizures in about two thirds of patients in which excision of cerebral scars was undertaken after first determining the trigger point' by means of electrical stimulation The necessity of an excision extensive enough to control seizures must be weighed against the possibility of a residual hemiplegia or aphasia Apparently a mere trephine opening or the separation of adhesions between the brain and meninges is of little avail Enucleation of a circumscribed tumor may be both life and seizure saving General surgery may be useful in removing infected or malformed organs or tissues which may be contributory elements in seizures

The correction of abnormalities in the digestive, endocrine circulatory and other systems requires the procedures of general medicine Poor posture should receive specific attention by the use of exercises to strengthen the abdominal muscles and instructions in correct standing Constipation requires the use of fruits and vegetables in the diet, regularity in bowel habits, exercise and possibly mild catharsis

A low metabolic rate may be brought to normal by the use of thyroid Hyoglycemia if present and if due to excessive insulin production calls for a low carbohydrate intake but if severe enough to be accompanied by symptoms of hypoglycemia surgical intervention may be necessary Disturbances of the sympathetic nervous system which so many patients exhibit can sometimes be helped through physical training and improvement of the general physique Though an emotional disturbance is only a contributing cause, its elimination may greatly improve the patient s lot The difficulty usually is near the surface financial or domestic worries, feelings of incompetency fear unfulfilled ambitions conflicts between parental and personal desires These situations should be exposed and righted

Raising the Seizure Threshold—Diet, dehydration and drugs are three practical methods of increasing a patient s resistance to seizures Patients should eat what the other members of the family eat if their diet is sensible and well balanced The exception to this rule is the use of the ketogenic diet in children This diet is expensive and distasteful and long continued use calls for fortitude and intelligent cooperation on the part of patient and family Out of 267 children treated by Helmholtz 47 per cent were improved The book by Talbot gives details of this form of treatment

Dehydration—Dehydration secured by reduction of fluid intake was first advocated by Fay In order to produce a net loss of tissue fluids the total fluid intake must be reduced to 20 ounces or less a day not counting the water content of solid food The check on effectiveness is a decrease in body weight with the total caloric intake remaining the same As a rough check on

ings or laryngospasm and the characteristic carpopedal spasm with pronation of hands and feet. Chovstek s and Trousseau s signs and the Erb electrical reaction are positive the roentgen ray may show a beginning healing of rachitis, the serum calcium is low and the phosphorus high

Treatment consists of administration of calcium chloride 15 to 30 grains (1-2 Gm) four to six times a day or viosterol 15 to 20 minims (1-2 cc) twice a day with exposure to the sun or ultraviolet light

WILLIAM G LENNOX

ECLAMPSIA

Toxemia is an important complication of pregnancy occurring in about one tenth of pregnancies and accounting for about one fourth of maternal deaths The term is used to cover various conditions acute yellow atrophy of the liver nephritis hypertension of pregnancy, pernicious vomiting mild and severe preeclampsia and eclampsia itself

Symptoms.—Convulsions are the distinguishing feature of eclampsia Eclampsia occurs in about 0.2 per cent of pregnancies in about 1 per cent of maternity cases in hospitals and in about 2 per cent of patients with some form of toxemia of pregnancy It is unusually common in primiparous patients in twin pregnancies and in the presence of hydramnios

Etiology —A discussion of causes must include two conditions first the so-called toxemia and second the eclampsia which would seem to be only a superadded symptom There is an ominously large number of explanations for toxemia uremia bacterial auto intoxication biological reactions toxic substances from the fetus or the placenta endocrine disturbances mammary toxemia dietary alterations physicochemical changes Each of these theories has had its proponents

As for the eclampsia presumably patients with toxemia who become eclamptic have a tendency toward convulsive reactions If so they should have a cerebral dysrhythmia which antedates the pregnancy also eclampsia and epilepsy should appear with unusual frequency in the same person or in an unusual number of relatives especially in identical twins These questions have been insufficiently studied

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harm In children the use of a hot bath is irrational but if the child is feverish, a cold sponge bath is indicated

MAINTENANCE OF MENTAL HEALTH AND USEFULNESS —The prevention of physical and mental stagnation requires the institution of active measures There must be regular and sufficient time for eating and sleeping vigorous exercise, and, if possible, participation in interesting and worthwhile work Seizures come most frequently when body and mind are idle Driving an automobile and certain dangerous occupations are taboo but the risks inherent in many sports and occupations are less to be feared than psychologic invalidism Children should, if possible, continue in school

Many patients suffer more from the fear of seizures than from the seizures themselves The patient and those about him should look on seizures, not as a catastrophe but as a temporarily disabling condition like migraine, or dysmenorrhea or an impediment of speech The physician can point to the fact that the great majority of patients with seizures are leading fairly normal lives and that many, in spite of epilepsy, have attained distinction Patients need to be protected from discouragement from the horror of school authorities or employers who wish to discharge them forthwith and from the overprotection of relatives The public needs to be educated away from the idea that epilepsy is a hopeless mentally deteriorating disease Not always, or often, can the physician stop seizures, but *almost always* he can inspire new courage and build morale Furthermore joined with others, he can educate patients and the public to a more just and hopeful attitude about epilepsy Enlistment of the support of patients and their friends and relatives is possible through the Laymen's League Against Epilepsy

INSTITUTIONAL CARE —Many persons with epilepsy need to be segregated from the general population and provided for in hostels or hospitals At present eleven of the states provide well equipped buildings and commodious grounds equipped to care for an aggregate of 18 000 of the approximately 60 000 patients in institutions These colonies are havens of refuge for persons who are hopelessly deteriorated or who cannot be kept at home without unduly sacrificing the needs of other members of the family There is great need for private but moderate priced care of patients who *should not* be sent to state institutions

WILLIAM G LENNOX

SPASMOPHILIA

In children with seizures acquired and genetic factors may seem inextricably mixed The earlier in life seizures begin the greater seems to be the factor of inheritance and developmental defects of the brain and birth injuries are additional loads which cause an immature and inadequately insulated nervous system to break into a convulsion In children, even more than in adults, a combination of causes may be responsible Peterman assigned one cause for seizures in each one of 911 children ten years of age or under Various causes were acute infections 35 2 per cent epilepsy and unknown 25 3 per cent, cerebral birth injury 16 4 per cent, spasmophilia or tetany 8 7 per cent, miscellaneous 8 3 per cent and meningitis encephalitis, and whooping cough 6 1 per cent Spasmophilia was reported *only* in children during their first three years or in 12 per cent of a group of 659 children of that age A convulsion in early childhood *especially* if repeated must be regarded with some uneasiness Thom gathered information about 8823 children in a laboring population During their first five years approximately 7 per cent had one or more seizures Of this group 12 per cent and of the total goup 0 8 per cent later became epileptic a ratio of 15 to 1

Spasmophilia is a term used for childhood tetany The subject of tetany is fully discussed elsewhere Undoubtedly the diagnosis of spasmophilia is often made on insufficient grounds as suggested by the frequency with which children with this diagnosis later become epileptic

The etiology is much the same as that of tetany Affected children are often rachitic In babies symptoms are often precipitated by lack of respiratory control especially in the presence of respiratory infections

Symptoms are irritability facial twitch

ings or laryngospasm and the characteristic carpopedal spasm with pronation of hands and feet Chovstek s and Trousseau's signs and the Erb electrical reaction are positive, the roentgen ray may show a beginning healing of rachitis the serum calcium is low and the phosphorus high

Treatment consists of administration of calcium chloride 15 to 30 grains (1–2 Gm) four to six times a day or viosterol 15 to 20 minims (1–2 cc) twice a day with exposure to the sun or ultraviolet light

WILLIAM G LENNOX

ECLAMPSIA

Toxemia is an important complication of pregnancy, occurring in about one tenth of pregnancies and accounting for about one-fourth of maternal deaths The term is used to cover various conditions acute yellow atrophy of the liver, nephritis hypertension of pregnancy, pernicious vomiting mild and severe preeclampsia and eclampsia itself

Symptoms.—Convulsions are the distinguishing feature of eclampsia Eclampsia occurs in about 0.2 per cent of pregnancies in about 1 per cent of maternity cases in hospitals and in about 2 per cent of patients with some form of toxemia of pregnancy It is unusually common in primiparous patients in twin pregnancies and in the presence of hydramnios

Etiology.—A discussion of causes must include two conditions first the so called toxemia and second the eclampsia which would seem to be only a superadded symptom There is an ominously large number of explanations for toxemia uremia bacterial auto intoxication biological reactions toxic substances from the fetus or the placenta endocrine disturbances mammary toxemia dietary alterations physicochemical changes Each of these theories has had its proponents

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tem with a congenital or acquired irritability

Symptoms —Symptoms of toxemia which usually precede the appearance of eclampsia are albuminuria, hypertension edema visual disturbance, nausea and vomiting and headache The convulsion unlike the epileptic seizure has a gradual onset with twitching of the small muscles of the face and slow extension to the rest of the body The convulsions are severe, bilateral tonic clonic and not distinguishable from the *grand mal* of epilepsy Apparently *petit mal* or psychomotor seizures are not a part of the eclamptic syndrome Usually convulsions are few in number but may be multiple similar to a *status epilepticus*

Diagnosis —In approximately one half of the cases the convulsions occur before labor and in one fourth they occur either during or after This consideration together with a *history of symptoms of toxemia makes the* diagnosis simple Confusion may arise when convulsions occur in an epileptic at or near labor

Prognosis —Maternal mortality ranges between 10 and 25 per cent with the lower figures in recent years and child mortality *around 40 per cent Maternal mortality is* higher with antepartum eclampsia and with unskilled treatment. The maternal prognosis is best in young women

Treatment —Observation throughout pregnancy should detect the toxemia in its early stages when treatment can be most *effectively applied* The use of progesterone and estrogen is logical but too expensive at present When eclampsia sets in active treatment and constant nursing care is necessary The decreased mortality of recent years is attributed to the substitution of conservative delaying tactics for the formerly popular method of immediate emptying of the uterus During the period of convulsions the primary objectives are adequate sedation and increased urinary output For the first morphia is the drug of choice Plass advocates giving morphine only hypodermically in doses of ¼ grain (0 016 Gm) repeated at intervals until the respiratory rate is reduced to twelve per minute This may require from 1 to 1½ grains (0 065 to 0 1 Gm) This sedation may be supplemented by chloral hydrate 30 grains (2 Gm.) in 100 cc of milk For the promotion of urinary excretion, intravenous injections of 500 cc of a 10 to 25 per cent solution of dextrose are most effective or 20 cc of a 10 per cent magnesium sulfate solution may be given intravenously using no more than five injections in twenty four hours From 200 to 400 cc of blood may be withdrawn for the sake of reducing blood pressure. Bryant and Flemming had only two deaths in 120 patients with the use of veratrum viride magnesium and glucose solutions intravenously and sedatives for extreme restlessness Veratrum viride is a powerful *vasodilator and must be used with caution* giving 10 minims (0 6 cc) immediately and repeating it every 10 to 15 minutes until the pulse rate is below sixty or blood pressure is below 120 systolic thereafter, until the patient is conscious 3 to 10 minims (0.2 to 0 6 cc) doses are given if the pulse rate exceeds *eighty or the blood pressure exceeds 150* systolic Whatever drug therapy is used gentle handling rest and quiet are of primary importance The patient should not be rushed to a distant hospital If comatose she must be fed by nasal tube with carbohydrates and a minimum of protein When the *convulsions are over and the patient* has regained consciousness and strength, she should be delivered as a means of preserving the life of the fetus If the fetus is dead haste is less urgent because fetal death has a favorable influence on the course of the eclampsia

William G Lennox

SYNCOPE

Fainting is considered here because of the frequency with which it is confused with epilepsy It is a common symptom Although especially frequent during adolescence and among females it may occur at any age Approximately one *adult in 200 faints* on the occasion of acting as a blood donor The syncope is directly due to cerebral anemia The underlying factors are variable The first is a certain constitutional susceptibility evidenced by a family history of fainting Contributory are conditions which place a strain on the sympathetic nervous system fatigue hunger standing immobile, pain migraine headache and emotional shock

such as the sight of blood or of others fainting The experimental studies of Weiss suggest that there is first a dilatation of veins and a pooling of blood in them increase in heart rate decrease in pulse pressure loss of consciousness a fall of the body to the prone position with reestablishment of an adequate supply of blood to the heart and restoration of consciousness. Fainting may however occur when the person is lying down it may be accompanied by cyanosis and jerking of extremities and be followed by vomiting features which suggest epilepsy especially if the electroencephalogram is abnormal Attacks which are at first syncopal may later become epileptic Usually however the tendency to faint disappears with the passing years The various disorders of circulation with which fainting may be associated are discussed elsewhere A person who has fainted should be allowed to lie quietly and recover spontaneously For prevention the cause or causes must be ascertained and appropriate treatment instituted For patients with orthostatic hypotension or vasomotor instability building a vigorous physique avoidance of fatigue smoking and drugs like sodium nitrite which interfere with normal vascular responses often prove helpful

WILLIAM G LENNOX

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MIGRAINE

Definition.—Migraine is a periodic cephalalgia characterized by the absence of any local lesions which might cause headache and peculiar as regards the visual and oculoplegic symptoms and psychic phenomena which may accompany it. All migraine except that of the abdominal type may be considered headache, but all headache is not migraine Migraine is characteristically periodic but in the majority of instances the attacks occur irregularly with no definite interval between the crises The term ophthalmic migraine' is somewhat superfluous because it is merely a separate name for the periodic headache associated with such visual disturbances as transient scintillating scotomata

Etiology—Migraine can be shown to be hereditary in every instance if heterozygous inheritance is carefully considered There is also a kinship between migraine and epilepsy and Buchanan s statistics seem to indicate that an individual with migraine is more likely to produce epileptic offspring than is an individual with epilepsy

In the old conceptions migraine was explained on the basis of injury excessive work or exhausting disease but new ideas have relegated such factors to secondary place Excesses of work and the ill effect of exhausting disease can be fully corrected without relieving the migrainous constitutional syndrome As Miller and Raulston point out there is evidence to support the theory that migraine is allergic in nature and therefore in some measure comparable to hay fever asthma and urticaria Patients with migraine frequently have periods of relative immunity during which nervous strain such as ordinarily brings on an attack is without effect These might be considered refractory periods corresponding to an antianaphylactic state and they emphasize the points of similarity between asthma

which is certainly allergic, and migraine. In each, the attacks are periodic nervous influences are important in precipitating an attack, the disturbance frequently disappears temporarily after some prolonged infection, and pregnancy sometimes exerts a favorable influence A certain kind of food has been known to precipitate an attack in both conditions Migraine as well as asthma is often accompanied by eosinophilia These points at most suggest by analogy that migraine is an allergic disease Brown believes that in migraine the condition of the gastro intestinal tract and the character of the diet play at least a secondary or contributory role in producing the explosive phenomena. He divides cases of migraine into four groups (1) those associated with intake of more carbohydrate than can be utilized, (2) those associated with the intake of animal food either in excess or of a type which sets up a specific reaction (3) those few associated with true intestinal toxemia caused by the decomposition products of protein digestion which are possibly related to histamine and (4) those associated with metabolic abnormalities which require complete avoidance of purine containing foods Timme says that two classes of food invariably precipitate attacks in predisposed individuals, *i e* substances rich in iodine such as fish, oysters clams and occasionally spinach and carbohydrates in excess

Foldes believes that migraine is due to increased water retention in meningeal and cerebral tissues but it has been shown that forced fluids and injections of pitressin do not induce headache.

Kennedy gives reasons for believing the migraine attack is due to localized meningeal and cerebral edema on the tentorial shelf causing visual phenomena in the sphenoidal fissure causing compression of issuing nerves and Charcot s ophthalmoplegic syndrome There are studies giving evidence which associates the hypophysis and the ovary with the migrainous attack The joint factual evidence was the demonstration that the presence of prolan in the urine is definitely related to the occurrence of the migrainous seizures Prolan has also been found in the urine of males with migraine

Women are two or three times more susceptible to migraine than men

Morbid Anatomy—The pathology of true migraine is not known at present, and probably cannot be fully discovered until the correlation of the sympathetic nervous system and the endocrine system is better known and the phenomena of allergy are better understood Graham and Wolff have carried out recent experiments which bear upon the mechanism of migraine and the origin of migraine pain They have demonstrated that changes in the intensity of migraine headache are related closely to changes in the amplitude of pulsations of branches of the external carotid arteries Their data lend support to the postulate that the pain is produced by distention of cranial arteries, a view quite at variance with the former conception that vascular spasm might be a factor Obviously the next step is to seek the origin of the arterial distention

Symptoms—Just before an attack of migraine the patient may experience vague feelings of impending malaise for a variable number of hours Severe pains of great intensity then develop sometimes gradually and sometimes with great suddenness They are usually intense across the forehead but may be focused back of or between the eyes or be entirely occipital or temporal and limited to one side In any individual the pain is usually in the same place in every attack. It is severe incapacitating and made worse by such environmental annoyances as jarring movements bright lights and loud sounds During this period there are sometimes flashes of light or dark and light spots before the eyes or scintillating zigzag lights The visual acuity may become dimmed or the visual fields contracted Partial oculomotor paralysis with temporary strabismus sometimes occurs and in rare instances peculiar odors or tastes slight hemiplegia or temporary aphasia has been noted Transitory states of mild confusion with apparent disturbances of perception may develop It has not been shown that these are not due to the mental abstraction which the suffering occasions Vertigo and a distressing tinnitus are frequently seen and nausea often followed by vomiting is a common symptom

Disturbances of the sympathetic system are evidenced by pallor coldness and sweating of the hands and feet unilateral hyper

idrosis pupillary fixation (either dilatation or marked contraction) excessive lacrimal secretion, and abnormal salivary secretion The gastro-intestinal symptoms are probably *referable to the sympathetic system* In most cases they are associated with relatively mild cephalic pain although the usual visual and vertiginous disturbances are present with localization of the severe pain in the abdomen

The attack is never febrile It is not accompanied by leukocytosis but in a large percentage of cases there is temporary eosinophilia (5 to 16 per cent) The pulse may be slow

The attacks usually last one to three days occasionally only a few hours They recur at varying intervals once or twice a month and even weekly and in women are apt to coincide with the menses At the menopause *they are very likely to disappear In rarer* instances the menopause marks the inauguration of migraine not previously present.

In a few cases (about 7.5 per cent) epilepsy and migraine are coexistent. The epilepsy may come in major attacks but manifestations of petit mal are more usual in this association

Treatment —The initial treatment is the establishment of suitable personal hygiene Sufficient and regular sleep regularity of meals avoidance of strain and worry are essential Toxic infections of the tonsils teeth sinuses and intestines must be corrected For the attack itself proper conditions of solitude and quiet may be supplemented by *such simple procedures* as cold and hot compresses the menthol stick and hot foot baths.

Aspirin and other sedatives may be given but morphine and its derivatives should *never* be used in migraine because of the danger of addiction

The administration of calcium lactate by mouth (30 grain doses) with the approach of symptoms may abort an attack Phenobarbital mildly beneficial during the attack may also be *of value in the interval between* attacks in delaying their return The drug most apt to relieve the largest number of patients is ergotamine tartrate (trade name gynergen) an alkaloid of ergot Brock O Sullivan and Young confirm the work of others with this agent. In a majority of patients, subcutaneous injection of 0.5 to 1 cc (0.25 mg.–0.5 mg) causes the headache to disappear in one to three hours Vomiting often accompanies relief The drug may be *given orally in 1 mg doses but subcutaneous* use is more effective However, at times the taking of 1 mg, two or four times a day orally in tablets during the symptom free interval lessens the attacks in frequency and intensity

A therapeutic measure sponsored by Alvarez and which may come to rival gynergen in efficacy is the inhalation of 100 per cent oxygen All one needs is a tank of oxygen an inhalation apparatus a reducing valve and a flow meter The amount of oxygen used is usually between 6 and 8 liters per minute Both cephalic and abdominal migraine have been relieved and attacks terminated within an hour or two

Sluder s cocainization of the sphenopalatine ganglion may relieve atypical cases A procedure based on the allergic conception is the intravenous injection of from 0.5 to 2 cc. of a 5 per cent solution of peptone (Miller and Raulston) Injections starting at 0.5 cc are usually given twice a week but the intervals are gradually lengthened to a month If the medication is discontinued the migraine sooner or later returns the longest period of freedom after discontinuance being nine months.

Finally there is endocrine therapy Pituitary extract (whole gland substance 0 1–1 grain once or thrice daily one hour after meals) may prevent attacks A daily divided *dosage of 5 cc of amniotin (2000 rat units)* orally relieves more than 50 per cent of cases The induction of an artificial menopause by the use of radium has cured some patients

THOMAS K. DAVIS

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or more peripheral branches of the trigeminal nerve They are most common about the nose and mouth These hypersensitive zones are usually referred to as 'trigger zones' since touching them precipitates an attack of pain

The disease usually begins in middle life or later, but occasionally has occurred among children The pain appears periodically lasts for a few weeks is followed by intervals of relief extending from a few weeks to six months. At first the pain may be located along the distribution of one of the branches of the trigeminal nerve but as the disease progresses it extends to involve two branches and occasionally the third The mandibular and superior maxillary branches are affected most commonly but it is not uncommon for the ophthalmic branch to be involved also The particular arrangement of the involvement is not constant however As the disease progresses the symptoms increase in severity and duration The intervals of relief become shorter until the pain is almost continuous. At first the patients are rarely disturbed with pain at night whereas in the advanced stages of the disease the slightest contact with the trigger zone results in the precipitation of a paroxysmal attack

Complications.—Occasionally a boring like pain in the superior maxilla with projection down the neck and shoulder a condition known as *Sluder's neuralgia* is mistaken for the pain of trigeminal neuralgia The pain from neuritis which follows dental operation or caries likewise has been mistaken for trigeminal pain Thus it should be borne in mind that unless the patient has a paroxysmal type of pain with a trigger zone the disease is not trigeminal neuralgia The treatment of these two similar types of pain is not as effective as is the treatment of trigeminal neuralgia Not infrequently patients of advanced years who have cerebral arteriosclerosis complain of a dull aching burning and drawing sensation of the gums and face These symptoms may appear independently of trigeminal neuralgia but are usually associated with it The paroxysmal attacks of pain may be so severe that the patient fails to describe this unpleasant sensation until he has been relieved of the paroxysmal attacks for these continuous dull aching drawing pains are not relieved by injection of alcohol or by section of the sensory root

Diagnosis—Trigeminal neuralgia is accompanied by definite symptoms that are not readily confused with other pains of the face The pain is characteristically periodic, severe of short duration (a few seconds to a minute or two), occurs during waking hours is brought on by external irritation, is almost always unilateral, and differs from the dull aching continuous type associated with *dental caries* or *sinus infection* Furthermore deep alcoholic injection of the trigeminal branches as they leave the skull affords temporary relief and produces anesthesia of the region supplied by those nerves This does not occur with other types of pain of the face

Prognosis and Treatment.—The disease at first is intermittent, but the pain gradually becomes more persistent until it is almost continuous affecting first one branch then a second and often a third and being present in one or all three branches simultaneously It has never been known to disappear permanently without operative interference and while drugs and other kinds of treatment have been thought to afford relief the cessation of the pain during the administration of the particular form of treatment was probably merely a coincidence

The two accepted measures for *palliative treatment* consist of peripheral avulsion and *deep injections of alcohol* in the branches of the trigeminal nerve as they leave the skull. The average duration of relief following *peripheral avulsion* is eight months avulsion cannot be repeated The *deep alcohol injection* which is the best palliative therapeutic procedure affords continuous relief for an average of eighteen months The procedure is not altogether free from complications but proves successful in about 75 per cent of cases and can be repeated a number of times The technic described by Levy and Baudouin and modified by Patrick in 1907 is generally used

The needle consists of a trocar and cannula, 8 cm. in length and 1.5 mm in diameter graduated in centimeters the blunt end is constructed to permit the attachment of a 5-cc syringe The area to be injected is prepared as for surgery The patient is given nitrous oxide until analgesia ensues The needle may

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THE NEURALGIAS

Neuralgia' is a term applied to painful sensations that extend along one or more of the cranial or spinal nerves Neuralgia occurs in paroxysms in contrast to neuritic pain which is more or less continuous Neuralgia is probably the result of central lesions whereas neuritis is the result of peripheral involvement

TRIGEMINAL NEURALGIA

(Trifacial Neuralgia Tic Douloureux)

In trigeminal neuralgia it once was thought that only the gasserian ganglion was affected However the disease probably is of a more complicated nature involving not only the gasserian ganglion but also the root of the trigeminal nerve and its connection with other nerve cells affecting one or more branches of the trigeminal nerve It is manifested by sharp shooting excruciating pains The disease usually begins in middle life The pain appears periodically lasting for a few weeks and in the beginning is followed by intervals of relief of from four to six months In increases in severity and duration as the disease progresses and the intervals of relief become shorter until the pain is almost continuous

History—Trigeminal neuralgia was first described by Avicenna, an Arabian physician as *tortura facies* (facial agony) Previous to 1900 various medical remedies (aconite belladonna and opium) were used in the treatment, but with little success In 1891 Horsley and Krause devised their operation for ganglionectomy through the transtemporal route and in 1898 Hutchinson advocated partial resection of the ganglion Spiller in 1898 advocated division of the sensory root of the gasserian ganglion in lieu of radical removal Frazier and Spiller in 1901 proved that division of the sensory root was fully as efficacious as gangliopectomy It was learned later that Horsley also had employed division of the sensory root for trigeminal neuralgia and apparently had performed it prior to Frazier's operation In 1902 Petres and Verger and in 1903 Schlosser described methods of injecting the peripheral branches of the fifth nerve and the gasserian ganglion with alcohol At about the same time, Cushing developed a technic for dividing the sensory root, and also perfected the technic for avulsing the ganglion Since then the palliative treatment has consisted of alcohol injection and peripheral avulsion and the radical treatment of division of the sensory root. There have been minor changes in the operation but most surgeons follow the principles laid down in the physiologic extirpation or division of the sensory root, which gives permanent and instant relief from the neuralgic pains

Etiology—Frazier and Dana were of the opinion that the disease was the result of a lesion situated in the gasserian ganglion Frazier thought the disease was the result of a sclerosing process Dana attributed it to degenerative changes within the gasserian ganglion Horsley was of the opinion that trigeminal neuralgia resulted from an ascending neuritis caused by dental caries Unfortunately these early hypotheses have not been substantiated Even though section of the sensory nerve root or interruption of sensory impulses peripheral to the ganglion by section or injection does give relief from pain the pathologic lesion presumably is situated within the brain central to the trigeminal nerve The exact nature of the lesion is still unknown It has been postulated that the attacks of pain are related to some vascular disturbance. There is no evidence of hereditary tendency although more than one member of a family may be afflicted

Symptoms—The pain is described as shooting stabbing jabbing flash like darting zigzag lightning like and sizzling burning pain As a rule the attack is of short duration and is never continuous or of a dull aching type One severe attack may extend into the next one in such close order that pain may appear to be continuous for an hour or so at a time The attacks of pain are brought on by eating drinking talking exposure to sudden draughts or by washing the face and teeth Most patients complain of hypersensitive regions which involve one

extracranial avulsion of the glossopharyngeal nerve there was a sense of fulness on the side of the pharynx operated on complete anesthesia to pain temperature and tactile sensation over the entire half of the posterior aspect of the soft palate and anesthesia back to 1.5 cm from the posterior border of the upper aspect of the soft palate That portion of the pharynx between the level of the hard palate and the pyriform fossa was likewise anesthetic to pain tactile and temperature stimulation Sensations remained normal over the posterior half of the nasopharynx and over all of the nasopharynx below a line drawn through the hard palate as well as over the epiglottis and the upper aspect of the larynx The sensations of taste (salt, sweet, bitter and sour) were absent over the entire half of the tongue on the side operated on

Prognosis and Treatment—While the pain is primarily intermittent, it tends to recur until it is almost continuous It does not cease spontaneously On account of the position of the glossopharyngeal nerve and its intimate association with the hypoglossal nerve and vagus it is unwise to attempt an *injection of alcohol Intracranial division* proximal to the ganglia is necessary for permanent relief

ALFRED W ADSON

SCIATICA

The term sciatica' is applied to painful conditions of the sciatic nerve The condition has been considered an infectious lesion of the sciatic nerve Therefore the treatment has consisted in eradication of foci of infection and local application of heat However this conception has undergone a radical change during the last few years The fact that unilateral sciatica recurred and failed to respond to treatment employed for neuritis gave rise to investigations that revealed that protrusions of the nucleus pulposus from the intervertebral disks were the most common cause of unilateral sciatica It is true that the sciatic nerves their ganglia and roots are subject to the same lesions to which other nerves are subject and that when they are affected similar treatment is indicated

Before making a diagnosis of sciatica' due to a protruded disk one must differentiate sciatica from such lesions as hypertrophic arthritis, spondylolisthesis, sacralization of the fifth lumbar, anatomic anomalies pelvic tumors and intraspinal tumors which can and do produce local pain with radiation of pain along the sciatic nerve

Symptoms Produced by a Protruded Intervertebral Disk.—Patients who have protruded intervertebral disks in the lumbar and lumbosacral areas complain of localized tenderness muscle spasm scoliosis and a limp with radiations of pain along one or both sciatic nerves The recurrence of attacks with increasing severity and a failure of the patient to secure permanent relief from belts braces and physiotherapeutic measures strongly suggest the existence of a ruptured intervertebral disk with a protrusion or extrusion of the nucleus pulposus The majority of patients give a history of having sustained an injury which has resulted from lifting a heavy object falling and landing on the buttocks or having been more or less jackknifed in between two objects The initial pain is usually a sensation of a sharp sting in addition to the sensation that something has given way Frequently the initial symptoms subside upon bed rest and the application of heat with extension applied to the lower extremities The interval of relief may continue for several months when a slighter injury gives rise to a recurrence of a similar set of symptoms Occasionally patients are unable to recall having sustained any type of injury When this is true the onset is less abrupt but the symptoms may be just as severe as those that develop following a definite injury

As the patient presents himself for examination he complains of a limp and scoliosis with the thorax usually tilted away from the side of the lesion Tenderness is usually elicited in the lower part of the back near the sacro iliac joint and along the course of the sciatic nerve in the buttocks He usually objects to sitting in a chair and prefers to stand or lie with the thigh partially flexed The examination also reveals muscle spasm an inability to flex the thigh with the knee bent (Kernig s sign) and an inability to flex the thigh with the leg extended (Lasegue s sign) Patellar reflexes

then be inserted without pain until it strikes the nerve, when the patient indicates pain by resistance or movement Complete anesthesia is produced before all of the 5 cc of 98 per cent alcohol is injected

The radical treatment consists of injection of alcohol into the gasserian ganglion or of subtotal or complete section of the sensory root by the transtemporal or suboccipital approach The most serious objection to the injection of alcohol is that the procedure is carried out blindly and there is always danger that the alcohol may be injected into the subarachnoid space in the middle fossa and impair the function of the oculomotor nerves Therefore most surgeons choose to visualize the sensory root before sectioning it Since the disease so frequently spreads to other branches of the same nerve I prefer to divide the entire sensory root whenever branches other than the third are involved The present technic of transtemporal division of the root, with preservation of the motor root has been so perfected that the complications of keratitis or facial paralysis are rarely encountered The mortality is less than 0.5 per cent and the result is so gratifying to the patient that the radical operation should be advised and performed in all cases of trigeminal neuralgia At the onset of the disease I believe it is advisable to advocate deep injection of alcohol on one or two occasions as a therapeutic test and as an educational measure in order that the patient may appreciate the effects of numbness that result from injections of alcohol or division of the root and thus may be better prepared to accept the permanent numbness from the radical operation

Alfred W Adson

GLOSSOPHARYNGEAL NEURALGIA

Glossopharyngeal neuralgia is similar to trigeminal neuralgia in that the associated pains are spasmodic excruciating and lancinating but differs in that the pain radiates from the pharynx and tonsillar fossa to the ear The pain may be brought on by swallowing or yawning, lasts from a few seconds to a minute or two and recurs many times during the hour As in trigeminal neuralgia the attacks are intermittent but are of shorter duration and separated by longer intervals of relief

History.—In 1910 Weisenburg described the glossopharyngeal nerve syndromes and in 1920 Sicard and Robineau described 3 cases of "algie velo-pharyngée essentielle the first two of which were seen in the French Army in 1916 and 1917 In both the pain had persisted for several years and was not continuous but recurred frequently day and night in extremely acute paroxysms on the least movement of mastication deglutition or speech The patients developed suicidal tendencies on account of the apparent incurability of the condition They were treated by section of the glossopharyngeal nerve and the pharyngeal branches of the vagus and by ablation of the superior cervical sympathetic ganglion

Etiology—The causes of glossopharyngeal neuralgia are still unknown but are probably similar to those of trigeminal neuralgia Again relief is secured by interrupting the sensory impulse Temporary relief is obtained when the fibers are evulsed peripheral to the ganglion and permanent relief when the root is sectioned proximal to the ganglion through a craniotomy

Symptoms and Diagnosis—Glossopharyngeal neuralgia simulates trigeminal neuralgia in its occurrence, duration repetition and character but differs from it in its distribution and the location of a trigger zone in the tonsillar fossa It is more often brought on by swallowing than by chewing cannot be evoked by rubbing the face and only occasionally by rubbing the ear It also differs from trigeminal neuralgia in that the pain radiates from the pharynx and tonsillar area through the neck to the ear particularly to the tympanum It is possible to evoke paroxysms of pain by stimulating the pharynx but difficult to produce them if the pharynx and tonsillar area have been thoroughly cocainized such anesthesia does not inhibit paroxysms of pain in the maxillary and mandibular branches of the trigeminal nerve in *trigeminal neuralgia* Glossopharyngeal neuralgia also is unlike trigeminal neuralgia since it is impossible to inject the nerve with alcohol because of its close proximity to the vagus hypoglossal and spinal accessory nerves Temporary relief can be obtained however by peripheral avulsion just as in trigeminal neuralgia

Doyle emphasizes the diagnostic symptoms and also the sensory and gustatory changes in glossopharyngeal neuralgia and states that in two patients who had had

extracranial avulsion of the glossopharyngeal nerve there was a sense of fulness on the side of the pharynx operated on, complete *anesthesia to pain, temperature and tactile* sensation over the entire half of the posterior aspect of the soft palate and anesthesia back to 1.5 cm from the posterior border of the upper aspect of the soft palate That portion of the pharynx between the level of the hard palate and the pyriform fossa was likewise *anesthetic to pain tactile and temperature stimulation* Sensations remained normal over the posterior half of the nasopharynx and over all of the nasopharynx below a line drawn through the hard palate as well as over the epiglottis and the upper aspect of the larynx The sensations of taste *(salt sweet bitter and sour)* were absent over the entire half of the tongue on the side operated on

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ALFRED W ADSON

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Before making a diagnosis of sciatica" due to a protruded disk, one must differentiate sciatica from such lesions as hypertrophic arthritis, *spondylolisthesis*, sacralization of the fifth lumbar, anatomic anomalies, pelvic tumors and intraspinal tumors which can and do produce local pain with radiation of pain along the sciatic nerve

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are usually normal, but the Achilles' reflex is usually reduced or absent

Aside from the usual symptoms produced by protrusions of ruptured intervertebral disks at one or more levels, unilateral or bi lateral, the occasional patient may complain of localized tenderness and spinal rigidity with none of the radiating symptoms with negative Kernig s and Lasegue s signs and normal reflexes Not infrequently patients with the classical symptoms may have ac companying paresthesias and anesthesias along the lateral distribution of the leg and foot In a few isolated instances the patient s chief complaint was pain and paresthesia along the lateral aspect of the leg and foot with none of the other classical symptoms Several patients have had the usual symp toms but in addition they have complained of peroneal anesthesia and an inability to urinate Therefore roentgenographic inves-tigation has been necessary in order to recog nize a lesion Variation in symptoms is usu ally due to a migration of the extruded nu cleus pulposus The majority of protrusions occur lateral to the posterior longitudinal ligament they occasionally occur in the mid line thus producing pressure on several sac ral nerves rather than on a single nerve root The size of the protruded mass likewise changes the degree of compression of ad-jacent nerve roots, and in exaggerated cases a hypertrophied ligamentum flavum may be responsible for compressing more than one nerve

The variability of symptoms produced by a small protrusion of the intervertebral disk compressing one nerve root against the pedicle of the vertebra and a group of symp toms resulting from an extrusion of the nu cleus pulposus into the spinal canal sub-stantiate the argument that investigation cannot be too thorough The variability of symptoms therefore justifies myelographic studies with one of the following media oxygen oxygen combined with helium air or radiopaque oil (pantopaque or lipiodol) The latter two media may give rise to radic-ulitis and should be removed when possible, either following the study or at the time of the operation Chemical studies of the cerebrospinal fluid which frequently reveal increased protein in the presence of pro-truded disks were once thought to be sig nificant but later they have proved to be of less value in the diagnosis since chronic protruded disks can exist without producing changes in the cerebrospinal fluid

In selecting patients for surgical treat ment all means of investigation should be used in arriving at an accurate diagnosis Surgery should not be advised at the onset of the symptoms until conservative meas ures have been tried since undoubtedly slight lacerations in the annulus fibrosus heal by scar and spontaneous, permanent recov eries result Surgery should be resorted to in the acute case when symptoms fail to subside with palliative measures and is also indicated when recurrent episodes occur which incapacitate the patient Neurologic surgery without myelographic study is justi fied when the patient presents the classical history and neurologic findings However when in the presence of active hypertrophic arthritis of the lumbar portion of the spinal column or the sacro iliac joints the neuro logic and myelographic findings are not diag nostic neurologic surgery should not be ad vised on the basis of the symptoms alone

In view of the fact that an occasional protruded disk may not be visualized during myelographic study though still capable of producing symptoms when protruded (that is when producing a bulge of the annulus fibrosus with the patient in certain posi tions) the orthopedic surgeon advising a fusion for hypertrophic arthritis may re quest an exploration of the suspected disk prior to but during the same operative pro cedure thus avoiding the embarrassment of secondary operation for the removal of the protruded disk when the symptoms fail to disappear following fusion

Diagnosis—The addition of a myelo graphic study of the lumbar spine to a care fully taken history and a thorough examina tion is usually sufficient to determine the presence or absence of a protruded disk Al though protruded disks give rise to sciatica one must also consider all the other possi bilities that can produce sciatic pain

Treatment—The radical treatment irre-spective of the cause of sciatic pain con sists of removing the cause For example in the case in which a protruded disk is the causative factor the object of the operation is to remove the mass of fibromucoid car

tilaginous tissue which bulges through a tear in the intervertebral disk in order to eliminate the trauma to one or more nerve roots which are caught and squeezed between the protruding mass and the osseous and ligamentous structures of the spinal column

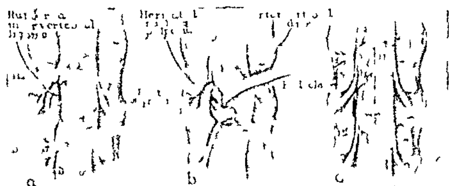


Fig 194—Compression of the nerve root by protrusion of the nucleus pulposus into the spinal canal and the relief of compression when the mass has been removed a protrusion of the nucleus pulposus through a rent in the intervertebral ligament, compression of the lumbar nerve root, b removal of the ribbon fibrocartilaginous nucleus pulposus c relief of compression of the nerve and dura following removal of the fibrocartilaginous mass

The *palliative treatment in the acute* condition usually requires bed rest and sedatives A firm mattress (boards under the mattress) is more comfortable than an innerspring mattress Buck's extension and local heat offer additional relief Preventive treatment

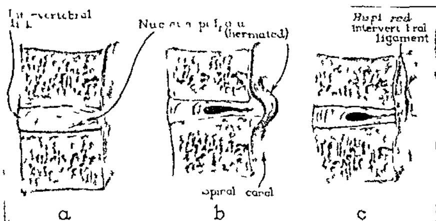


Fig 195—The mechanics involved in the rupture of the intervertebral disk with prolapse of the nucleus pulposus a normal intervertebral disk b prolapse of the nucleus pulposus into the spinal canal c, appearance of the ruptured intervertebral disk following removal of the prolapsed nucleus pulposus

during the interval between attacks consists of caution in avoiding the movements responsible for the attack Lumbosacral belts with Cook s shingle or close fitting canvas lumbar belts offer additional protection

ALFRED W ADSON

CERVICO OCCIPITAL NEURALGIA

Cervico-occipital neuralgia is a painful affection of the four upper cervical nerves chiefly of the great occipital branch of the posterior division of the second cervical nerve

Etiology—Although the cause is similar to that of sciatic and intercostal neuralgia that is, a *focus of infection* or an *acute infection* and occasionally *exposure* the disease is probably due to *specific infection of the dorsal ganglia* of the four upper cervical nerves

Symptoms.—The symptoms are excruciating more or less jabbing *pain* which radiates over the area supplied by the occipital nerve and *muscular spasms* and *stiffness of the neck* The skin over this area is highly sensitive to touch The point of greatest ten

derness is at the exit of the occipital nerve, which is approximately halfway between the mastoid process and the first cervical vertebra Next in order are the areas over the parietal eminence and between the sternomastoid and trapezius muscles

Diagnosis—The diagnosis is often confused with the neuritis due to *cervical arthritis* The differentiating diagnostic features in cervico occipital neuralgia are the primary affection of the occipital nerve and the intensity of the pain The characteristic posture of patients suffering from this disease is slight flexion of the neck with the head held rigid and the hand placed apprehensively at the back of the head to prevent the sensitive area from being touched Cervico occipital neuralgia is generally unilateral but it may be bilateral cervical neuritis with arthritis is usually bilateral

Prognosis and Treatment—The disease persists for several months and may then disappear if the infection has been removed It may recur much as does sciatic neuralgia

The *treatment* consists of removal of all *foci of infection* and local application of *counterirritants* *Injection* of alcohol into the cervical roots, as they leave the spine is frequently resorted to but is rarely successful *Anodynes* and *hypnotics* are necessary to alleviate the pain, if these fail *intraspinal division of the sensory roots* becomes necessary

Alfred W Adson

OTHER NEURALGIAS

Intercostal Neuralgia—Intercostal neuralgia is a painful affection of the intercostal nerves which may occur without an eruption of the skin as seen in herpes zoster Attacks of pain are paroxysmal and may return at intervals for many years Occasionally the primary attack never subsides *Palliative treatment* in the form of physiotherapy offers some relief but cannot be applied in the presence of eruption of the skin Frequently the *subarachnoid injection* of small quantities of *absolute alcohol* is effective in controlling the pain No more than 12 minims should ever be injected at any one time The injection should never be done unless the patient is placed on an operating table and the pillow so adjusted that the painful roots are on the upper side at the apex of the spinal curve In this position the droplets of alcohol may ascend through the spinal fluid to reach the sensory fibers of the involved nerve roots In most instances the subarachnoid injection of alcohol for *postherpetic pain* is a most satisfactory procedure but it may fail to produce relief in the intermittent type of intercostal neuralgia when herpes has not been present *Rhizotomy* and even *chordotomy* have failed to produce relief in this same group of cases

Atypical Neuralgia—Atypical neuralgia includes the various types usually classified in textbooks of medicine as *definite neuralgias* The term atypical neuralgia is used because in many instances the pain is due to neuritis or is referred along certain nerves as the result of various organic diseases and anatomic anomalies

Brachial Neuralgia— Brachial neuralgia is a term applied to the condition in which there is pain over the area supplied by the four lower cervical and the first thoracic nerves tenderness in the axilla over the deltoid behind the elbow, and in front of the wrist The pain is dull and aching and may persist for a few weeks to a few months, or longer

Lumbo Abdominal Neuralgia—Lumbo abdominal neuralgia affects the posterior fibers of the lumbar plexus particularly in the ilioscrotal region The pain is usually unilateral in the region of the iliac crest or along the inguinal canal in the spermatic cord in the scrotum or around the anus It is sometimes associated with a sacral neuralgia and causes the patient to complain of pain around the anus and the perineum

Coccygodynia—Coccygodynia is regarded as neuralgia of the coccygeal plexus It is generally considered a functional disorder although it is occasionally attributed to injury of the coccyx It is more common in women than in men and is aggravated by a sitting posture The disease is extremely difficult to cure

Phrenic Neuralgia—Phrenic neuralgia usually occurs in the lower part of the thorax but may be referred to the supraclavicular region of the neck The pain is aggravated by breathing movements coughing and deglutition and is usually associated with

diaphragmatic pleurisy or pericarditis In all probability it is due to a form of neuritis

Visceral Neuralgia.—Visceral neuralgia is more common in women than in men and is often associated with neurasthenia and hysteria The pain is usually in the pelvic region particularly around the ovaries but the gastro intestinal tract and kidneys may be affected The cause of the pain is questionable, since it is difficult to demonstrate a lesion in the organs affected or in the nerves supplying them

Neuralgias of the Nerves of the Feet.—Cases of neuralgia of the nerves of the feet are divided into three groups *Group 1 painful heel* painful heel is equally common in men and women and is so severe as to interfere with walking It is thought to be due to bony spurs or to gonococcal infection evidence of arthritis is not always present *Group 2 plantar neuralgia* the pain in plantar neuralgia is associated with numbness tingling and hyperesthesia in the tips of the toe and in the ball of the great toe Occasionally there is sweating on the plantar surface of the foot This phenomenon thought by Drs Henderson and Adson to be of vasospastic origin is relieved by sympathetic ganglionectomy *Group 3 metatarsalgia* metatarsalgia is described by Morton as a painful affection of the fourth metatarsophalangeal articulation he ascribes it to pinching of the metatarsal nerve Relief is usually afforded by operative intervention.

Sluder's Neuralgia.—Sluder's neuralgia is a painful affection of the sphenopalatine ganglion which causes what Sluder calls a lower half headache' with boring and burning pain in the superior maxillary region and a radiation of the pain into the neck and the shoulder It is frequently associated with ophthalmic migraine Sluder has been able to relieve certain of these conditions by the injection of alcohol and phenol into the sphenopalatine ganglion

Otalgia and Mastoidalgia.—Lillie describes otalgia and mastoidalgia as pain in the region of the ear and of the mastoid without any obvious evidence of inflammation. Wilson believes that they are brought about by a referred pain along the auriculo temporal nerve

ALFRED W ADSON

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PROFESSIONAL CRAMP

A professional cramp is a special form of occupation neurosis Cerebral in origin it is best described as a focal fatigue ataxia. In mechanism it is allied to tic and especially to stuttering The commonest variety is the so called writer's cramp' though we also meet with similar conditions in the cramp of typists, cutters telegraphers cigar makers and so on Every type of musician has been the subject of this condition It shows itself in an inability to use a part, usually a hand or arm to do a particular movement The extremity is normal for all motor actions except the particular one When a person is learning an occupation he risks no cramp of the kind under discussion When he is expert and is having to repeat a movement over and over for long hours at a time he may develop it The patient with writer s cramp may no longer be able to write with a pen though able to use his hands and fingers skilfully in playing a piano This is because there is a cerebral fatigue not a muscular fatigue to blame At first the patient may have only a weakness or slight cramping which makes the full completion of the movement difficult Later the difficulty may be an effective paralysis of the hand when the particular movement is attempted In some instances tremor may be added to the situation when the patient is endeavoring particularly to overcome it

True professional cramp is free from the sensory or vasomotor signs of neuritic disease and leaves the muscles normal in contour and substance Occasionally slight grades of neuritis may develop as a coexisting difficulty

The chronic character of a majority of cases of professional cramp needs emphasis In treatment a temporary or permanent change in occupation is required with well apportioned diversion At this point motor activity of the affected parts for all movements in general should be insisted upon Physiotherapy and general tonic hygienic treatment are indicated, the former best directed not alone to the parts disabled Mental conflicts, important etiologic factors in some instances must be solved by mental analysis, freudian or otherwise In writer s cramp the introduction of different motor maneuvers, such as writing with more shoulder movement and less wrist, is helpful and often it is wise to have the patient train himself to use the other hand These shifts in the form of the motor endeavor need to be encouraged In all cure is sought along lines of reeducation combined with physiotherapy *and skillfully controlled rest Drugs are not* indicated except as placebos Some cases fortunately come to a spontaneous quiescence

Thomas K Davis

THE NEUROSES OR THE PSYCHO NEUROSES

Introduction —It *is* difficult in the present state of knowledge to define precisely what is meant by the term neurosis Essentially this is due to lack of knowledge of the ultimate cause or causes, but the difficulty also derives from confusion of terminology and conflict of points of view While it is obviously impossible to discuss in a few pages the many theoretic questions involved a few general considerations are necessary for the understanding of the *problem* For practical purposes it is perhaps better to look upon the neuroses as one large group as a *congeries of symptoms* or syndromes or disease entities which have varied manifestations, but which have a number of underlying factors more or less common to all of them

At the present moment two schools of thought dominate the field One which defends the psychologic or psycho*pathologic* point of view, the other which adheres to the organic somatic or pathophysiologic theory of the *neuroses A third approach* is the one which attempts to correlate the two seeing that it is impossible to define the *problem* either in purely psychologic or purely somatic terms However great the temptation and the justification for such correlation it must be admitted that we are as yet unable

to speak of physiologic processes in psychologic terms or of psychologic processes in physiologic terms It is to be feared that much of the prevailing confusion is the result of such attempts None the less numerous studies in what is known as psychosomatic medicine have sought to explore the field between psychiatry and internal medicine

Obviously the practising physician is primarily interested in the medical aspects of the neuroses namely, their etiology symptomatology and treatment and is prone to lay emphasis on the organic or pathologic point of view So too is the neurologist whose primary emphasis is on structure and function But there are a number of psychologic, more particularly psychoanalytic concepts without which it is impossible to give any modern formulation of the psychoneuroses Before proceeding therefore and to avoid undue repetition it may be well to define a few general concepts particularly those relating to mental mechanisms or psychodynamics

Psychopathology postulates the existence of unconscious mental processes which motivate normal as well as abnormal behavior and are regarded as the source of neurotic symptoms That is there is a *dynamic unconscious* the repository of experiences dating back to infancy which may come into *conflict* with objective reality and within which conflict may on occasion arise. This unconscious with its ideas cravings and groups of ideas or complexes is conceived of as being charged with energy derived from primitive impulses The energy directly traceable to sex impulses psychoanalysis terms the *libido* It is the restlessness of this primitive emotion which makes the unconscious dynamic The theory of the libido is not quite so strictly adhered to now and has also been considerably expanded In addition to the unconscious there is assumed the existence of a *preconscious* or subliminal state which unconsciously motivated ideas must pass before they can reach *consciousness* Here we have a theoretic scheme of *mental topography*

By a *complex* is understood an unconscious group of ideas charged with various emotions The psychologic importance of complexes lies in the assumption that they influence conduct indirectly and therefore in inexplicable ways The two psychoanalytically best known and most disputed are the *castration complex* and the *Oedipus complex* The former is understood to represent an infantile phantasy about the loss of the phallus or the threat against it the latter embodies identification with the parent of the same sex and a hostile intent against that parent with the desire of displacing him or her in the affection of the parent of the opposite sex To prevent the emergence of incompatible unconscious ideas which are apt to engender conflict a higher force is assumed to exist, that is there is *resistance* The process of submerging unconscious ideas is known as *repression*

The primitive emotional energy is regarded as capable of investing various parts of the body and of being arrested as it were at various stages of infantile development The former is spoken of as *cathexis* and the latter as *fixation* The stages or loci at which the libido is arrested are known as *points of fixation* among which may be mentioned the oral anal and genital That which attaches to the ego is known as auto erotic or *narcissistic libido* But this energy can be shifted from the ego to objects and persons outside it the process of shifting from person to person is spoken of as *transference* The return of the libido to earlier points of fixation, the withdrawal in the unconscious to infantile modes of behavior to lower levels of adaptation is known as *regression* But emotions may be detached from objectionable ideas and attached to such as can pass conscious censorship , and we then get *displacement* of affect Occasionally repressed ideas are regarded as belonging to other persons that is they are *projected* This mechanism of shifting onto others fears and wishes belonging to oneself is more commonly observed in the psychoses Sometimes emotionally toned ideas or complexes are withdrawn into logic tight compartments within the unconscious and there results *dissociation* of incompatible or contradictory ideas Another mental process utilized by the unconscious for the purpose of giving plausibility to incongruous ideas is *rationalization* This has been defined by Hart as a process of self deception by means of adventitious reasons '

Dissociation of affect or of the energy of the libido its shifting to low somatic levels and its attachment to bodily organs so that it may give rise to signs and symptoms is known as *conversion* *Ambivalence* is the existence side by side within the unconscious of ideas surcharged with opposite emotional tones, for example, love and hate or regard and contempt Occasionally one observes what is termed as *compromise formation'* in which there is partial gratification of conflicting emotional impulses In many normal people and most labile neurotics there is the tendency of the mind toward *identification* with persons representing ideals such as parents and teachers Another mental mechanism is that of *reaction formation*, with which is generally associated that of *compensation* Herein is involved a process of *substitution* of one set of acceptable ideas or actions for the very opposite which actually characterize an individual Finally there is the process of *sublimation* which consists of the vicarious gratification of sex impulses by their substitution with or direction into asexual socially useful aims

Psychopathology puts considerable emphasis on the significance of *dreams* and phantasies or primitive wishes in the mental economy Psychoanalysis regards the dream as representing the fulfilment of an unconscious wish The surface story is spoken of as the *manifest content* the underlying psychic process is the *latent content* The latter requires interpretation which is always carried out by means of *free association* and sometimes by the use of symbols Characteristic of the dream is its tendency to the transformation of stimuli into visual images to the condensation or distortion of ideas and images to the displacement of emphasis and to dramatization Most important is the lack of logic temporal or moral consistency *Autistic thinking* is a neurotic sort of daydreaming

To round out the psychoanalytic structure there remains the mention of what are known as metapsychologic concepts Among these are the *pain pleasure principle* and the *reality principle* each respectively characterizing unconscious infantile thinking and adult conscious behavior Then there is the conception of the unconscious *id* the *ego* or real ego and the *superego* or ego ideal Finally, there is the division of *ego* or *self preservation instincts* from *sex* or *procreative instincts* and the postulation of a *death instinct*

Without attempting adequate explanations, the various concepts enumerated have been introduced in order to illustrate the language of psychopathology Among the fundamental psychoanalytic concepts must be included the theories of a dynamic unconscious of unconscious conflict, of repression transference and infantile sexuality Whether one accepts or rejects the various theoretic concepts a knowledge of them is imperative for the discussion of the neuroses from a psychopathologic point of view

Etiology—Underlying every theory of the neuroses is the assumption that there is an indefinable hereditary or constitutional factor which plays the ultimate role in their causation Naturally those who hold to the organic point of view put greater emphasis on the constitutional factor while those who adhere more strictly to psychopathology lay the major stress on development and environment conditions At the present time it is not known what is the precise relationship of heredity to the neuroses what is the ratio between inherent predisposition and environment, nor what is the exact mode of their interaction The most, therefore that can be said is that heredity is one important cause, but whether it be a neuropathic or psychopathic" constitution a degenerative' tendency psychosexual predisposition defective *anlage* or what not we are unable to state

The *pathologic theory of the neuroses* postulates the existence of molecular biochemical or physical alterations in the nervous system with consequent disturbance of function to account for the physical signs and mental symptoms These changes are assumed to be the result of exhaustion or fatigue of the nervous system Among the causes invoked may be mentioned intense fear or fright other emotional shock prolonged starvation, excessive masturbation trauma to the head alcoholism infectious diseases and various acute and chronic intoxications whether endogenous or exogenous While this theory may account for some few neuroses and the causative factors assumed may serve to initiate or precipitate

a few others they certainly cannot be held responsible for all

The *physiologic theory* seeks to account for the neuroses by the assumption that there is interference with the normal functions of the brain, that is they are the result of excessive stimulation or inhibition which interferes with the passage of impulses over synaptic junctions and gives rise to dissociation either at high psychic or low physiologic levels While there is no doubt some truth in this view and it leaves out of consideration some vital etiologic factors it involves a number of theoretic postulates among them inhibition which is not even definable The *behavioristic theory* is one phase of the psychologic concept of the neuroses and is merely a verbal formulation of the physiology of conditioned reflexes Behaviorism assumes the establishment of motor behavior patterns and their gradual integration from infancy onward and conceives of the neuroses or anomalies of behavior either as failures of integration or as results of disintegration Here again one may accept all the facts of conditioned reflexes yet be unable to build a comprehensive theory of the neuroses on a few profound observations

The *endocrine theory* seeks to correlate disturbances in the function of the glands of internal secretion with the mental and physical symptoms of the neuroses For this there is a great deal of anatomic physiologic pharmacologic and clinical evidence Some of signs and symptoms of mild hyper- and hypothyroidism adrenemia dyspituitarism and dysfunction of the gonads bear close resemblance to those of the neuroses Certainly the occurrence of neuroses in relation to puberty menstruation pregnancy and the menopause is significant of the influence of the endocrines on psychic life. Conversely many of the signs and symptoms commonly seen in pure psychoneuroses are also found as early manifestations of definite disease of the glands of internal secretion There is therefore undoubted etiologic relationship of some kind but it is impossible in the present state of knowledge to define that relationship The same may be said of the relationship of the *vegetative nervous system* Here too the anatomic and functional relation of the hypothalamic vegetative centers of the brain and the nervous manifestations of impairment of the parasympathetic and sympathetic systems argue strongly for the vegetative theory of the neuroses Furthermore the so-called "vaso vagal crises bear close resemblance to the paroxysms of anxiety hysteria For the present, however, one can do little more than speculate Psychosomatic investigations concern themselves particularly with this field

One of the most widely held views is that the neuroses are caused by *suggestion* By suggestion is understood the inculcation and ready acceptance, without proof of propositions which have no logical basis and are contrary to reason Whether this state of rapport be one of dissociation a prestige relationship a propensity to sympathetic identification or a libidinal process as psychoanalysis would have it, the fact is that most people are suggestible to varying degrees and that neurotic symptoms can be brought about as well as dispelled by means of suggestion Unfortunately we cannot precisely state what suggestion is and how it works and when we state that a person is hysteric because he is suggestible and suggestible because he is hysteric we are merely begging the whole question

The *social biologic theory* seeks to explain the neuroses in terms of the conflict which frequently results from the inability of certain individuals to adjust to the environment and the social group within which they live The struggle between the primitive impulses or instinctive drives of the individual and the equally insistent restraints of a complex social order may lead to flight from reality and an evasion of the demands of life This is particularly true when it comes to the powerful sex instinct which chafes under the restraint that ethics morality and legal and social codes have set up Times of social stress such as wars famines economic and other upheavals frequently result in crops of neuroses among individuals who cannot meet the severe tasks to which they are subjected So too inability to submit to authority or discipline to break parental attachments to adjust properly to love life, to submit to the rules of the marital state or to conform to religious rituals all may lead to conflict and to neurosis as an escape from the struggle

Psychoanalysis postulates the existence

of an innate psychosexual predisposition which, if it comes into conflict with the environment *during the developmental age* and later in life gives rise to neurotic reactions Accordingly three steps are regarded as essential predisposition, situation and conflict Furthermore, persistence of infantile trends and abnormal psychosexual development are the characteristics of the neurotic And it is true that in general the neurotic is sensitive, self centered given to phantasy attached to mother suggestible, emotionally unstable inadequate immature, and incapable of adjustment to sex and love life on an adult basis Frequently he is narcissistic and auto erotic his sex impulses are infantile fixed at levels to which he regresses when adjustment to life in the face of difficulties becomes impossible

The unconscious dynamics then of a neurosis are as follows *external conflict* because of difficulties in adjustment to adult love life, withdrawal into phantasy and *regression repression* as the answer to frustration *inner conflict* and symptom formation The neurosis is regarded as the result of failure of repression and inability to resolve inner conflicts Metapsychologically speaking *the neurotic is sick because the super* ego frustrates the wishes of the unconscious (the id) The symptoms are explained in terms of regression of the libido Then too there is dissociation of the affective mental currents within the unconscious Where there is regression to infantile sexual patterns but no repression or inner conflict, the result is not a neurosis but a *perversion*

To sum up we have the pathologic theory of the neuroses the physiologic the endocrinologic vegetative physiologic behavioristic dissociation or suggestion social-biologic and psychoanalytic In the first, emphasis is put on organic changes in the next four on disturbance of organic functions in the last three on pure psychologic *mechanisms* An hereditary constitutional predisposition is assumed in all theories except possibly the behavioristic with this distinction, that psychoanalysis refers to an innate psychosexual predisposition The latter *alone assumes* the existence of a dynamic unconscious as the seat of conflict of infantile impulses

Classification of the neuroses obviously is important not only from the point of view of diagnosis but from that of prognosis and *treatment* However, owing to the multiplicity and complexity of clinical and theoretic views it is difficult to make one general classification Actually it matters comparatively little what classification one adopts, although here I shall follow the freudian, provided one maintains a fairly consistent point of view But even so, it is well to bear in mind that clinically one does not often meet with sharply circumscribed entities that more often one encounters syndromes which partake of various nosologic groupings that anxiety as a symptom colors most of the neuroses and that borderline and transition cases not only between the neuroses but between them and the psychoses, are quite common

The Neuroses

(*A*) Actual or organ neuroses
- I Anxiety neurosis
- II Neurasthenia
- III Hypochondria
- IV Traumatic neurosis (?)

(*B*) Psychoneuroses regression or fixation neuroses
- I Transference neuroses
  - (*a*) Hysteria
    - 1 Conversion hysteria
    - 2 Anxiety hysteria (phobias)
  - (*b*) *Compulsion neurosis* (obsession)
- II Other regression neuroses
  - (*a*) Perversion
  - (*b*) Character types erotic obsessional narcissistic
  - (*c*) Neurotic types (nonpsychoanalytical concepts)
    - 1 Introvert, schizoid
    - 2 Extrovert, cycloid

(*C*) Mixed neuroses
(*D*) *Borderline cases*

It is assumed that there is no regression in the organ neuroses but that there is a specific trauma" an actual disturbance of physiologic function and a psychologic reaction to it *Anxiety neurosis* is conceived of as the direct result of sexual frustration Wherefore it is observed in adolescent virgins in young adults who indulge in erotic stimulation without coitus in frustration by fear of pregnancy, coitus interruptus or ejaculatio praecox or abrupt cessation of masturbation and in cases of unendurable continence The attack of unmotivated anxiety is characterized by fears of death insanity heart disease or some impending calamity and is accompanied by palpitation tremor faintness dyspnea, dizziness etc

Neurasthenia is restricted by many psychiatrists to a syndrome which is characterized by lack of mental and physical vigor Lack of potency or ejaculatio praecox chronicity hypochondriacal symptoms and general fatigability constitute practically the whole picture Generally the patient is narcissistic but anxiety is usually lacking Altogether it simulates incipient organic diseases The syndrome rarely occurs in women *Hypochondria* is characterized by fixed almost delusional preoccupation with symptoms referring to bodily organs Anxiety frequently accompanies the syndrome which most commonly occurs in women often at the menopause age *Traumatic neurosis* is an ego rather than a psychosexual neurosis following injury generally to the head and is characterized essentially by subjective complaints such as headache dizziness loss of memory lack of power of concentration frightening dreams and a host of others

In addition to conflict and regression the psychoneuroses manifest efforts at restitution somatic conversion signs and symptoms psychologically elaborated anxiety and *phobias* consisting of unconsciously detached anxiety projected upon persons or things *Compulsion neurosis* (also known as *psychasthenia*) represents a further stage of regression to unconscious homosexual levels and an intellectual elaboration of defenses against the fulfilment of tabooed impulses Anxiety generally is lacking unless the compulsion is not allowed expression or the obsession paralyzes activity It is narcissistic neurosis *Neurotic character* represents a problem in social adjustment The *constitutional psychopath* belongs to this group and illustrates the influence of heredity The *introvert* is the subjective individual who is preoccupied with his own phantasies the *schizoid* is an exaggerated unsociable introvert The *autistic* type is Bleuler's concept of the introvert The *extrovert* is the sociable group man who deals in externals The *syntonic* is the integrated individual and the *cycloid* the one who oscillates between elation and depression The *borderline cases* between the neuroses and psychoses represent those wherein the symptoms partake of the nature of both entities Thus a deep hypochondria may simulate a psychotic delusion a compulsion a schizophrenic state and a neurotic depression a manic-depressive psychosis The title *mixed neuroses* sufficiently describes the group

Perversions which show regression but no repression conflict or symptom formation, are not true psychoneuroses There are partial and complete innate and acquired tendencies to perversion *Masturbation* while not a perversion in itself may become so if practiced inveterately and as an end in itself Mild degrees of 'perversion' characterize normal sex life *Masochism* expresses itself in sexual enjoyment of suffering *sadism* in the sexual gratification by infliction of pain *Exhibitionism* consists of sexual gratification from exposure of the genitals *Fetishism* is the enjoyment of objects endowed with sexual meaning *Homosexuality* is the practice of the sexual act with persons of one s own sex Among other perverted relations may be mentioned intercrural oral and anal (*pederasty*) practised mainly by the male *cunnilinguism* and *fellatio* the former more common among males the latter among females *Bestiality* denotes the practice with animals *necrophilia* with dead bodies *Incest* is the relationship with blood relations There is something of the compulsion in the perversions They seem to increase among intellectuals and in cultured societies They are seen among mental defectives and the insane and are apt to crop out under the influence of alcohol

In summary it may be reemphasized that psychopathology permits of no rigid classification that mixed neuroses are fairly common that there is a constitutional factor a character make-up in all neuroses and that in every neurosis one may observe considerable evidence of normal character and attempts at adjustment in addition to various psychopathologic phenomena Finally, to avoid giving an erroneous impression it may be stated that the possession of a mild neurosis or neurotic character or even an outspoken neurosis is not necessarily incompatible with social adjustment or even great usefulness Numerous artists and scientists and a host of others who have contributed to progress have suffered from inner conflict and been highly neurotic Nonetheless the psychoneuroses present a very difficult problem perhaps more important socially than that presented by the psychoses

Symptomatology—*Anxiety* is the most common symptom of the neuroses It constitutes the whole syndrome of anxiety neurosis, completely colors anxiety hysteria is the outstanding feature in phobias is frequent in hypochondria sometimes intense in melancholia and other depressive psychoses and may be seen in compulsions or obsessions Despite the apparent absence of motivation and the ridiculousness of the fear, the patient is helpless before his vague anxiety or the fear of death disaster, heart failure, insanity cancer, apoplexy, and so forth The anxiety may arise spontaneously by day or wake the patient out of sleep The *heart generally beats violently* there is a choking sensation in the throat breathing is rapid there is trembling faintness and a *feeling of impending dissolution or insanity* The patient appears anxious perspires, feels his body and limbs numb and he may be nauseated and have the desire to urinate or defecate After a shorter or longer period, with or without medical assistance the attack gradually tapers off *Hysteric anxiety* is apt to be more intense and accompanied by conversion phenomena (*q v*), also there is *more psychic* elaboration Insomnia and false vertigo frequently coexist *Pavor nocturnus* represents an hysteric anxiety attack and so does the *nightmare*

Phobias are specific hysteric fears with definite ideational contents The phobia is supposed to represent an unconscious wish an emotion dissociated from a tabooed impulse and attached to a harmless idea It differs from a compulsion in that the latter is supposed to be a ceremonial designed as a defense against sex transgression However it is sometimes difficult to differentiate clinically between an obsession and a phobia Fear of snakes, mice, thunder lightning darkness and so on, represents specific phobias *Agoraphobia* signifies fear of open places, crossing streets and squares *Claustrophobia* is fear of closed places such as churches theaters subways or elevators *Mysophobia* is fear of dirt or contamination *Anthropophobia* is fear of men *erythrophobia* of blushing *zoophobia* of animals *pyrophobia* of fire, *phobophobia* of being afraid, *syphilophobia* of venereal disease

The *symptoms of neurasthenia* consist essentially of abnormal fatigability and exaggerated irritability The neurasthenic gets up tired in the morning, complains of muscular weakness, is irritated by noises cannot concentrate, complains of memory defect, and is preoccupied with physical ailments He has pressure on top of the head pain in the spine, dizziness, weakness of the eyes (*asthenopia*) and tiredness on effort *Orthostatic tachycardia* so-called *'neurocirculatory asthenia'* and *neurasthenia cordis* may be part of neurasthenia or hysteria Gastric atony and enteroptosis are not uncommon Most important, however, are the sexual disturbances Aside from chronic masturbation there are nocturnal emissions, spermatorrhea, futile erections ejaculatio praecox or complete impotence and, withal increased sexual desire *Wherefore the neurasthenic is gullible* as to treatment and frequently a victim of quacks

Hypochondria is a symptom which occurs *in mild form in the neuroses and in exaggerated form* in the psychoses It is a more or less delusional preoccupation with symptoms *referring to bodily organs particularly* the nose, mouth and tongue anus and genitals There is as a rule little insight into the symptom and it *yields practically not* at all to medication or other therapy Hypochondria is most common in middle age and in women at the menopause It may persist unchanged for years or be the forerunner of schizophrenia Anxiety occasionally accompanies it

Compulsion neurosis of which the compulsion is the active urge to do things and the obsession the ideational counterpart consists of impulses which seem like intellectual foreign bodies They appear meaningless and purposeless and occur in certain types of individuals The compulsion may set in early in life or occur at any age, following apparently trivial incidents Both the compulsion and the obsession which neither logic nor reason can cope with persist despite every effort to dislodge them The obsession may consist of the thought or wish to hurt oneself or others to jump off heights to blaspheme to doubt—*folie de doute*—to repeat numbers or count windows, to think that the nose ears or hands are growing large to fear contamination and to repeat words or phrases

The compulsion to act frequently takes

on the form of simple or complex ceremonious rituals In order not to soil himself the compulsive neurotic may repeatedly wash his hands to overcome doubts he will shut doors windows or gas jets to see if his nose is large look at every mirror, to prevent a calamity write down names walk along the curb touch things or count on his fingers It seems as if he does all these things to defend himself, to build a citadel around himself to prevent the expression of tabooed cravings, and to escape anxiety This *repetition compulsion* this making of rituals may manifest itself in extreme orderliness in arranging clothes, pillows chairs and other objects by day or on going to bed in attending to business eating drinking walking receiving guests, answering letters or telephone calls or making love The compulsive act takes on the form and force of a religious ritual or ceremonial The compulsion to steal is known as *kleptomania* to take drugs *toxicomania* to drink periodically *dipsomania* to start incendiary fires *pyromania* to pull out hairs *trichotillomania* The compulsion or obsession may be so severe as to paralyze all thinking and action yet it may disappear and reappear as inexplicably as it originally set in Generally it persists most stubbornly

The *signs* and *symptoms of hysteria* are numerous protean and kaleidoscopic They can simulate practically every organic affection While *monosymptomatic hysteria* is not rare, there are as a rule a number of varied manifestations important among which are mood character and personality changes anxiety states subjective sensations and objective somatic signs Hysteria may appear at any age but generally sets in early in life not infrequently in childhood It is rather more common in women The *hysteric personality* is infantile The individual *is* hypersensitive self-centered narcissistic moody impulsive somewhat histrionic and generally deficient in emotional control He is anxious fearful affectionate and resentful by turns exaggerates complaints loves to indulge in phantasy and is highly suggestible The male may be ardent though impotent the female passionate yet suffer from *vaginismus* or even be frigid and have disgust for the sexual act *Pseudologia phantastica* a certain childish make believe or even outright lying are not at all uncommon Psychologically speaking the hysteric reaction represents flight from reality and every hysteric is a sick person who suffers a great deal

Among the sensory symptoms *hysteric pains* of every variety and severity are very common So are hysteric *headaches* of which *clavus* the boring type is somewhat characteristic Special mention should be made of spinal pains and rigidity, particularly *coccygodynia* of breast pains or *mastodynia* and of abdominal and other pains simulating visceral diseases There are subjective surface pains or *dysesthesias* objective *paresthesias* and localized hyperesthesias which formerly used to be known as *hysterogenic zones* A very stubborn dysesthesia of the tongue—*glossodynia*—is frequently accompanied by fear of cancer itching about the vulva is not uncommon as a paresthesia *Acroparesthesia* consists of numbness and tingling of the distal portion of the limbs and is especially common in middle-aged women *Hysteric anesthesias* are generally the result of suggestion They follow no anatomic neural distribution but affect a functional part—half of the body and face including the mucous membranes limbs and parts of limbs—and include every form of sensation even the special senses

Hysteric anosmia includes the loss of sense of smell and the perception of irritative substances Among the visual disturbances are unilateral and more rarely bilateral *amaurosis* suddenly following emotional shock and lasting for hours days or months *Dyschromatopsia* or perversion of color sense is rare Hysteric amaurosis is fairly easily detected *Photophobia* and *blepharospasm* are not rare while hysteric *myopia* is less common *Micropsia* and *macropsia* may be hysteric symptoms and *monocular diplopia* is practically invariably hysteric in nature

Hysteric paralyses while not as common as formerly are still rather frequent The paralysis *involves functional parts and not* groups of muscles innervated by special nerves Reflexes are present and atrophy is generally absent, though contractions and vasomotor changes may appear later The hysteric hemiplegia is apt to be flaccid the

leg being dragged rather than circumducted The *important feature of hysteric paralyses* is the apparent indifference of the patient and the lack of effort to *move the part* *Glossolabial spasms* and hysteric *pseudoptosis* may coexist Hysteric *astasia-abasia* is *the inability to stand* or walk despite normal power of the legs on lying down The fear to walk may amount to a phobia Urinary *retention* may go along with hysteric leg palsies, also pseudoclonus *Pollakiuria* is a rather common hysteric symptom Hysteric *aphonia* is the most common psychogenic *palsy* The vocal cord is found paralyzed and the voice is very hoarse Hysteric *mutism* is much rarer and should be distinguished from negativism *Stammering* is rather common *Hysteric contractions* set in very late and may manifest themselves as flexion of the fingers or fixation at larger joints, as torticollis, scoliosis and so on They generally disappear under anesthesia

While *hyperkinesias* are coming to be regarded more and more as organic in origin there are *hysteric tremors spasms* and *tics* There is no such entity as hysteric chorea it is either the one or the other *Torticollis* is not rare but in every case dystonia should be ruled out Some of these movements are compulsive rather than hysteric in nature *Hiccup belching aerophagy* are fairly common hysteric symptoms *Globus hystericus* lump in the throat, is typical and *esophagospasm* not rare *Hysteric anorexia* is very common, *vomiting* fairly so and *bulimia* or gorging least so Hysteric borborygmi are sometimes encountered but *meteorism* is rare extremely rarely the latter takes the form of *pseudocyesis* Psychogenic *constipation* is extremely common *diarrhea* and *mucous colitis* occur spasmodically following emotional trauma The colitis can become a very stubborn affair *Oliguria* and *anuria* are never hysteric hence the need for detecting deception The same may be said of *hysteric fever* though it has been reported

Hysterics may mutilate themselves though not so commonly as malingerers and psychotics Fanatics sometimes do in religious frenzies *Dermographia* and *ecchymosis* are more common among hysterics Vasomotor disturbances such as blushing and redness are occasionally encountered while cyanosis and edema may be seen late in hysterically paralyzed limbs Mention may be made of *urticaria factitia* Vaginal *pruritus* may occur in response to masturbatory phantasies Rectal pruritus is not rare When the former occurs in middle aged women it is well to rule out diabetes or some local condition

Hysteric convulsions are quite rare, but rather typical when they occur Generally after a prodromal period of *excitability* anxiety and globus hystericus the patient suddenly goes off into a convulsion or falls without hurting himself There may be no warning at all The body is rigid frequently arched backward the hands are closed the jaws tightened, the legs extended While the convulsion is tonic the patient holds his breath and gets blue in the face The tongue is not bitten but the lips may be Nor is there incontinence though there may be purposeful urination There may be grimacing laughing, crying, howling barking, thrashing about or snapping and biting What is known as the *attitude passionnelle* represents an ecstatic coitus exhibition The attack may last a few minutes or pass over into status hystericus All the while the pupils react to light, though the patient may resist opening the eyelids and there is no true coma Never as in genuine convulsions is there a fixed or non reacting pupil a Babinski sign or posttraumatic headache and somnolence A sharp stimulus can put a stop to the convulsion Hysteric epilepsy is a definite misnomer

Occasionally one observes profound alteration of character amounting to complete splitting or *dissociation of personality* These states can be brought about in hypnosis but may occur spontaneously The simplest are the *automatisms* during which the patient carries out coordinated acts of which he is totally unaware in his normal state They may be seen after hysteric fits *Automatic writing* belongs in this group The hand seems to move spontaneously and to record lost memories or imaginary conversations Hysteric and other mediums indulge in this during seances Then there are the *amnesias* wherein the events of brief or long periods are totally forgotten The simplest is the *lacunar* or *circumscribed* form *Anterograde amnesia* denotes loss of memory after

the onset of the illness and *retrograde amnesia* the loss up to it These are not to be confused with true *amnesic aphasia* which is an organic brain condition *Tropic amnesia* or *coast memory* occurring among the whites on the West Coast of Africa, may possibly be hysteric in origin

Hysteric catalepsy manifests itself as a psychogenic fit The patient is speechless motionless rigid and the limbs are in the condition known as flexibilitas cerea Sensation is lost except for the corneal This state must be distinguished from catatonic rigidity Hysteric *lethargy* or *trance* is also known as *narcolepsy* It is like a profound hypnotic state The muscles are however relaxed and the patient may swallow food Indian fakirs and *mediums* can spontaneously go into these lethargic states The condition may simulate death though there is hardly danger of burial alive True narcolepsy is an organic condition occurring either idiopathically following encephalitis or in the course of tumors of the brain especially in the region of the third ventricle

Somnambulism is a brief hysteric dissociated state generally occurring at night during which the patient carries out automatic acts without being aware either at the time or on awakening The individual may unwittingly hurt himself during these nocturnal episodes The same state can be induced hypnotically *Hysteric fugues* are ambulatory automatisms lasting days or weeks and represent daydreaming adventures The patient may take long trips or carry out apparently responsible activities of which he is utterly unaware at the cessation of the fugue *Dual* or *alternating personality* is a hysteric splitting of character of long duration There is a complete change of personality with different states of consciousness The individual may assume a new name carry on an occupation wholly different from the one he left behind and after a long period suddenly awake to wonder what he is doing in his new environment Or the individual may find himself in a blank state not knowing his name or who he is We have thus a primary and secondary personality each unaware of the other that is there is *reciprocal amnesia* *Hypnagogic hallucinations* consist of momentary flashes of scenes or events occurring in the twilight states before falling asleep These may occur in normal as well as in hysteric individuals While it is doubtful whether there are hysteric psychoses there is hysteric depression The *Ganser syndrome* is regarded as a hysteric twilight state, occurring in prisoners and is characterized by dulness confusion and indifference to surroundings

Psychic impotence refers to the male *frigidity* to the female There are varying degrees of impotence, depending normally on time place and person Whereas impotence precludes coitus, frigidity does not Frigidity is not synonymous with psychic impotence, as the former implies either absolute lack of desire or actual aversion Both impotence and frigidity may occur in hysteria Neurasthenics and other chronic masturbators may suffer from ejaculatio praecox or complete impotence Frigidity is seen in conscious and unconscious female homosexuals Psychic impotence occurs in depressions Schizophrenics frequently are impotent or frigid Perversions may be caused by or result in impotence Psychic impotence with normal facultas coeundi but no orgasm is common in the female but extremely rare in the male

Occupation neuroses manifest themselves in inability to perform skilled acts learned by use despite absence of signs of involvement of the nerves or muscles supplying the parts They simulate apraxias without brain disease Thus a person may be unable to write though he can use his fingers to play the flute though he can pucker his lips whistle and so on to play the piano or typewrite though his fingers are otherwise skilful These conditions are generally regarded as hysteric in nature and indeed one frequently observes other phenomena which confirm the diagnosis But it is well to rule out apraxia incipient dystonia and other organic diseases of the nervous system Occupation neuroses are seen in typists telegraphers bookkeepers seamstresses watchmakers tailors blacksmiths and in piano violin and flute players always affecting the muscles most used in the particular occupation *Writer s cramp* is the most common occupation neurosis but before making the diagnosis one should always rule out an organic condition At first there is easy fatigability then difficulty in writing finally

total inability, requiring the training of the left hand or the substitution of typewriting It is a particularly stubborn condition sometimes necessitating change of occupation

War neurosis is the designation applied to a multitude of neurotic conditions observed in soldiers during the World War Other terms were *shell shock fright neurosis concussion neurosis neurocirculatory asthenia* None of these terms does more than superficially describe conditions which actually cannot be dignified as special nosologic entities Some of them like shell shock are misnomers At best they describe symptoms Many of the manifestations appeared in soldiers who were in camps behind the front, or received no injury at all even while engaged in combat On the other hand some followed temporary burial alive or occurred in close proximity to violent explosions The majority however were true hysteric manifestations Among the physical conversion signs may be mentioned paralyses astasia abasias and other gait anomalies stammering aphonias blindness deafness tremors palpitation sweating and anesthesias Among the mental symptoms were intense anxieties *fears phobias and terrifying dreams or nightmares* Essentially these signs and symptoms did not differ from those seen in civil practice Most of them were the result of auto or heterosuggestion in response to a desire to escape from a frightful experience They were unconscious defense reactions to immediate threats to life They were not conscious purposive flights from combat where they were the condition was that of malingering Evidently the threat was not to the sex but to the *ego instincts* Hence war neurosis may better be described as an ego neurosis But the mental mechanisms were the same inability to adjust to a situation *external conflict regression* repression inner conflict defense symptom formation flight from reality and escape from danger

Traumatic hysteria and *traumatic neurosis* are applied interchangeably to a group of symptoms following trauma Actually I believe they represent two psychologically and clinically distinct syndromes though their manifestations are almost identical Following some trifling or more serious trauma, often to the head in which there may or may not be a brief period of unconsciousness the patient develops a series of minor or major incapacitating signs and symptoms Sometimes these follow immediately after the accident at others there is an 'incubation period' of variable duration in which the individual is well and possibly able to return to work The actual symptoms, most of which are subjective and difficult to evaluate, are many and varied The most important and most persistent are *headache* and *dizziness* In addition there may be anxiety, depression irritability, general lack of vigor inability to concentrate impairment of memory noises in the ears and head faintness or fear of fainting feeling of numbness and various pains and aches Also there may be tremors, sweating palpitation, dyspnea flushing and possibly attacks of syncope In the case of traumatic hysteria there may be gross signs, such as staggering other bizarre gaits stammering and various palsies or anesthesias The pulse may be rapid the reflexes hyperactive the blood pressure low Sometimes nightmares occur during which the traumatic experience is relived

The following criteria may serve to distinguish between traumatic hysteria and traumatic neurosis Both are unconsciously motivated where they are not and the person consciously and purposely utilizes the injury for personal gain he is a malingerer But traumatic hysteria develops in a person who has been previously neurotic and of hysteric make up The trauma precipitates a series of symptoms in a person who is predisposed What happens is that the individual unconsciously utilizes the injury as a refuge from personal conflicts The symptoms may occur after trifling injury and in the absence of litigation Where the question of compensation enters it need not be regarded as the major role though it may play an important part both in the traumatic hysteria and in the neurosis Where litigation and compensation are the sole motives we are once more dealing with malingering In traumatic neurosis the hysteric mechanisms are lacking It probably is a true neurosis more of the nature of an ego neurosis It is possible that there is actual brain injury though where this is of a more or less definite

nature the term "traumatic encephalopathy" or "concussion of the brain" is the more suitable term In traumatic neurosis which most often follows injury to the head the *individuals suffer from intense anxiety and* nightmares reproducing the accident and they are unable to return to their usual occupation The condition is much the more stubborn, resisting all forms of therapy

All cases of trauma are complicated by the suggestibility of most individuals by desire to escape drudgery and by incentives to litigation But if one excludes the malingerers there remains the small traumatic encephalopathy group which is obviously organic in nature the hysteria and the traumatic neurosis All are precipitated by the trauma The first is also caused and maintained by it The traumatic hysteria is not truly caused by the injury and is unconsciously maintained by personal *difficulties for which the* accident serves as a spark without which there might not have been a lighting up of the process In traumatic neurosis the injury may be held strictly accountable Litigation may play a role but it is not the decisive one in either case In both instances we are dealing with sick people So-called compensation neurosis which comes dangerously close to malingering is in the words of Foster Kennedy an anxiety state born of fear nursed by litigation kept alive by greed and terminated by a verdict

Diagnosis —The diagnosis of the neuroses requires thorough neurologic and general medical knowledge no less than sound *psychiatric insight* The absence of organic signs and symptoms does not always imply the existence of a neurosis and their presence does not necessarily exclude its possibility Certainly the present state of knowledge does not justify the diagnosis of any neurosis by exclusion alone As a general rule it may be stated that no diagnosis of hysteria anxiety states or compulsions and obsessions should be made without effort to discover some underlying psychogenic factors because *it not infrequently* happens that a tumor of the brain a latent carcinoma an obscure anemia mild hyperthyroidism or incipient tuberculosis fail to show definite organic signs and sometimes mask themselves under a group of symptoms which are commonly regarded as neurotic So too it is well to bear in mind that a neurotic can develop organic disease which may be overlooked It is important therefore not only to begin with a thorough physical *examination but to reexamine* the patient from time to time This does not, however justify indiscriminate "work up" of cases with all sorts of irrelevant tests Sound clinical judgment is very often superior to so called "laboratory facts" While there are no absolute diagnostic criteria, intense individual study of each case a good detailed history not too much emphasis on isolated signs and symptoms proper evaluation of the whole clinical picture and understanding of the mental reactions and the social setting will serve as the best general guides Finally as most neuroses trace back to adolescence one should make with caution such a diagnosis in a person past forty who *has been well previously*

The diagnosis of the neuroses involves the differentiation of psychogenic from organic diseases of one neurosis from another of neuroses from borderline psychoses and of neuroses from malingering

Angina pectoris and other cardiovascular disease may be mistaken for anxiety neurosis or anxiety hysteria But while cardiac conditions are frequently accompanied by anxiety there is pain on exertion the distress is generally precordial the dyspnea genuine and the gastric distress peculiar and there are blood pressure variations electrocardiographic evidence and other definitely organic signs In the anxiety states on the other hand there are no heart signs other than the palpitation one may elicit a history of coitus interruptus fear of pregnancy other sexual frustration or conflict over masturbation the patient generally is young there may be a precipitating psychic factor and a history of previous attacks with remissions is not uncommon When a syndrome of so called "neurasthenia" appears in an adult or middle aged person who gives no antecedent history the following organic conditions should be ruled out

Cerebral arteriosclerosis is characterized in addition to mental symptoms by focal signs of brain damage retinal arteriosclerosis some hypertension cardiac enlargement and renal damage and definite memory impairment with character alteration In *Ad*

dison's disease there is marked hypotension severe asthenia loss of weight diarrhea, and bronzing of the skin and mucous membranes *General paresis* is a psychosis with special physical signs the Argyll Robertson pupil or other pupillary anomalies the speech disturbances, tremor of the lips the true psychotic manifestations and the positive blood and spinal fluid reactions are absolutely pathognomonic *Tumors of the brain* will ultimately be signalized by the typical headache, vertigo and vomiting by focal signs and symptoms, and by choked disk *Pernicious anemia* and *pulmonary tuberculosis need only to be mentioned* the blood picture and the x ray are sufficiently conclusive *Tuberculous spondylitis* and *cancer of the spine* however may lead to an erroneous diagnosis In the former the x ray is diagnostic in the latter time alone and clinical judgment decide *Multiple sclerosis* also occurs in the young and is characterized by remissions but the nystagmus Babinski sign absent abdominal reflexes tremors ataxia speech disturbances and other signs of *dissemination serve as diagnostic aids* With regard to the endocrinopathies it is well to bear in mind dyspituitarism adrenal, gonadal and thyroid insufficiency and hyperthyroidism Rapid pulse loss of weight ocular signs sweating and especially increase of basal metabolic rate should rule out incipient *Graves disease Acroparesthesia* occurs in women at the menopause age

There are so many conditions which give rise to *headache* that it is quite impossible to enumerate *them here Suffice it to say* that all efforts should be made to rule out organic disease, that *migraine* deserves special mention and that the psychogenic headache is more of a pain in the head or scalp It has already been stated that hystero epilepsy is not a true entity In any case, the true *convulsive state* whether petit or grand mal is characterized by absolute unconsciousness and the convulsion by falling with injury, tongue biting incontinence, *fixed* pupils and by subsequent headache and somnolence *Postepileptic confusional states* differ from hysteric *fugues* in their briefness suddenness violence sometimes *furor* absolute *amnesia and a history* of convulsions *Hysteric syncope* occurs in neurotic individuals after psychic trauma the unconsciousness is not very deep and the attack is brief

While there is no doubt of the existence of hysteric *dyskinesias especially tremors* spasms and tics, although the latter is more apt to be compulsive in nature, the burden of proof is on him who makes the diagnosis Organic dyskinesias may occur in the absence of all other signs It is doubtful whether myoclonus ever is hysteric in nature, certainly chorea, athetosis and dystonia never are Torticollis may be either In all *occupation neuroses* it is important to rule out neuritis, apraxia, tabes, syringomyelia *and dystonia Obviously, local* atrophies, sensory loss fibrillations and loss or increase of deep reflexes point to organic brain or cord disease *Hysteric vomiting* and *anorexia nervosa* may lead to diagnostic errors The history the comparative absence of loss of weight, the negative x ray and other findings and the general picture speak for the psychogenic disturbance Pituitary cachexia *Simmonds disease,* should be borne in mind

The *diagnosis of one neurosis from an other* is of importance as a guide *to treat*ment but, aside from the difficulties arising from lack of consistency as to classification the infrequency of pure' syndromes makes absolute differentiation rather difficult If the freudian view of *anxiety neurosis* is correct it should be limited to cases which are the result of psychosexual trauma such as coitus interruptus ejaculatio praecox forced abstinence dread of pregnancy conflict over masturbation and other sex frustrations In *anxiety hysteria there is greater* psychic elaboration the conflict is deeper unconscious conversion hysteric symptoms co exist and surface explanations do not help as in the neurosis Accepting *the freudian* concept the diagnosis of *neurasthenia* should be restricted to patients who suffer from loss of energy physical and mental fatigability pain in the back or *the head* and ejaculatio praecox or impotence all this whether there is a history of chronic masturbation (which there usually is) or not

The difference between a *phobia* and an *obsession* lies in this that the former is always characterized by the intense anxiety the latter by none or very little that the first is specifically emotional the second compulsively intellectual that the one is a

hysteric reaction masking an unconscious wish the other a ritual of defense, that the hysteric is a disorganized personality the compulsive often a superior intellectual with fixed traits that the phobia is more amenable to suggestion and other treatment than the obsession or compulsion However it may on occasion be very difficult to differentiate between them and the two may coexist The criteria for diagnosis of war neuroses and traumatic hysteria and neurosis have already been given under symptomatology The first and last are really ego neuroses and not psychoneuroses

The following clinical and psychologic criteria will serve to differentiate a severe *neurosis* from a mild *psychosis* The neurotic however sick he may be realizes the fact suffers from his symptoms makes effort to get well and keeps in touch with his environment Generally he is not antisocial The psychotic does not realize that he is sick hence sees no reason for seeking medical aid he has no insight into his condition has broken with his environment and become antisocial The delusions and hallucinations are very real to him and he projects onto others conflicts which rage within Thus for instance *competitive jealousy* is a properly motivated reaction to the threatened loss of a love object *projected jealousy* such as the false accusation of infidelity is a phantasy reaction to a possible situation *paranoid jealousy* directed to members of the same sex probably is a defense against unconscious homosexuality *Transient depressions* may occur in the neuroses, profound depression or melancholia with suicidal ideas only in the psychoses *Motivated depression* is an in between reaction

Schizophrenia or *dementia praecox* is progressively characterized by a shut in unsocial personality by overattachment and latent hostility to parents by ideas of reference and suspicions by delusions that the patient is watched plotted against persecuted or being poisoned by auditory hallucinations by negativism mannerisms catatonias or even stupor and by emotional poverty which indicates a splitting (whence the name schizophrenia) between the intellectual content and its appropriate emotional overtone The schizoid individual is really a *forme fruste* of the preceding but not necessarily psychotic The *hypochondriac symptom* is always delusional, but depending on its intensity and complexity and the degree of dominance over the individual it may occur either in the neuroses or the psychoses The *obsession* or *compulsion* may be so paralyzing as to appear delusional but in essence it is not, seeing that the patient has comparatively good insight into his general condition and realizes that he is sick

Malingering or *feigning* is more common with regard to psychoses The malingerer to evade responsibility, escape punishment or acquire gain simulates or exaggerates symptoms or diseases There is conscious purposive effort to deceive by means of imposture The malingerer alleges loss of memory deafness blindness or mutism and complains of subjective symptoms which cannot be evaluated He may simulate paralyses tremors or fits Generally he overdoes his stunts especially when he knows he is being observed The diagnosis of malingering is not always easy hence special tests or even tricks are utilized for purposes of detection Obviously the malingerer cannot feign true organic signs nor is he as a rule so well informed as to simulate consistently neurologic and psychiatric conditions

Course and Prognosis —These vary with the type of the neurosis and its duration with the environmental circumstances and the skill of the therapist The course is episodic and frequently characterized by remissions The prognosis is better in young persons than in old and confirmed neurotics in the flexible emotional type than in the rigid shut in personality *Anxiety neurosis* has a comparatively good prognosis provided the cause can be favorably influenced *Neurasthenia* is a stubborn condition difficult to cure in the young and almost impossible of resolution in confirmed masturbators who are impotent *Hypochondriac symptoms* are most refractory and persistent they occasionally subside spontaneously and more rarely pass over into true delusions

The prognosis in *hysteria* is most variable Anxiety symptoms and conversion signs are frequently cured Phobias are very stubborn Much depends on the skill of management Hysterias in children offer the best prognosis Generally speaking once a hysteric

always a hysteric, but remissions are very common and adjustment usually possible Compulsions and obsessions are extremely refractory to treatment Remissions are not uncommon The narcissistic neurosis generally begins early in childhood though it may be overlooked and often persists throughout a whole lifetime Sometimes the condition merges into a psychosis Complete cures are extremely rare but amelioration of symptoms is quite common Occupation neuroses have a more or less favorable prognosis The outlook in writer s cramp is not so good Very frequently the patient is compelled to give up his occupation Tics and spasms are not easily or favorably influenced even if they are psychogenic in nature Torticollis is a particularly stubborn affection

Treatment —The treatment of the neuroses requires in addition to knowledge and experience much tact and understanding and considerable self assurance Although psychoanalytic insight is invaluable and the method useful in selected cases there are a great many therapeutic measures which can be successfully employed The fact is that most neuroses are amenable to treatment certainly all of them can be managed intelligently even if a good many cannot be cured The most difficult to manage are old and confirmed neurotics unimpressionable and intensely narcissistic individuals and patients whose neuroses are rooted in insuperable social economic or familial situations Even so provided one can win the confidence of the patient much may be done to help him to understand the problem and to get him to adjust himself in some measure

Most neurotics are highly sensitive, wherefore it is necessary to make good contact on the first examination The most important thing to do is to get a detailed medical social and psychosexual history and follow it up with a thorough physical examination The first is for the purpose of gaining insight into the patient s condition and the second to eliminate the possibility of organic disease as well as to convince him that his complaints are taken seriously Both will beget confidence One must avoid the error of telling a patient that he imagines' he is sick or that the whole thing is mental and there is nothing the matter with him Neurotics resent the first and misinterpret the second In any case, a neurosis is just as much a sickness as any other disease and causes a good deal more suffering besides

If no evidence of organic disease is found the patient may be reassured on that point, but he must be promptly told that nervousness' is a medical condition which requires treatment like any other One may explain however, that psychic shock, such as fright worry and anxiety, or social conflict and sexual difficulties, can cause all sorts of subjective symptoms and objective signs Should some organic disease be discovered it is obviously necessary to treat it but one should be careful not to overemphasize the organic condition in a neurotic lest he cling to that and refuse to face the more important problem of the neurosis

Medicinal treatment has some value but no specific virtues As a matter of fact most neurotics show their lack of faith in medication by asking not to be given drugs or "dope" In many cases the value of the prescription is in direct proportion to the amount of suggestion it embodies Even though neurotic insomnia does not readily respond in hypnotics it is frequently necessary to prescribe phenobarbital allonal, amytal or some other preparation For sedative purposes chloral and bromide are useful Narcotics should be avoided because of the danger of addiction A warm bath often acts as a sedative A mild laxative may be given to overcome constipation or simple dietary rules laid down but enemas should be advised against because neurotics tend to become enslaved to them and make a ritual of colonic irrigations

Extracts of the *glands of internal secretion* may be prescribed where evidence of endocrine dysfunction is present Not that present knowledge justifies the indiscriminate prescription of the extracts for the neuroses certainly no phobia or compulsion has thus far been cured by any of them but there are instances where thyroid or pituitary extract is of value or even the extract of suprarenals and the more recent one of the ovaries The last especially theelin may be useful in the so called menopause neuroses Experience justifies the statement that re

moval of foci of infection has no effect in the vast majority of the neuroses Obvious infections should be treated of course but, aside from the fact that the whole theory has been tremendously overemphasized indiscriminate extraction of teeth excision of tonsils and other heroic operations only do violence to patients and confirm their neuroses

Except in cases of so-called colitis or where the problems of specific anaphylaxis and possibly of avitaminosis come into question *diets* seem to play no etiologic or other role in the neuroses That neurotics will slavishly follow dietary rules evolve weird ones of their own and make rituals of meals is no reason for prescribing special diets unless one wishes to embody suggestion thereby Even so one many only succeed in perpetuating symptoms Unless therefore there are special contraindications it is best to avoid undue emphasis on any diet and advise simple nourishing easily digestible foodstuff possibly rich in vitamins

Rest is of some value in anemic emaciated patients but *rest cures* have little to recommend them Sojourn in a hospital at a health farm sanatorium or spa may have temporary worth essentially this lies in sound routine and the power of suggestion The last is the main ingredient in places of religious pilgrimage Nonetheless temporary removal from home is frequently advisable even though the patient takes his inner difficulties with him and must return to his environmental ones *Massage* and *hydrotherapy* are sometimes indicated for their physical as well as for their psychotherapeutic effects *Occupation therapy* is also of some value particularly if intelligently directed so as to serve a useful purpose

It has already become clear that *suggestive therapeutics* is what one consciously or unconsciously employs with greatest effect in most cases no matter what form the treatment actually takes Whether suggestion be regarded as a prestige phenomenon a so called libido transference reaction or a simple emotional identification rapport the fact remains that it will favorably affect many of the neuroses and definitely succeed in removing individual symptoms Suggestion is most effective in the hysterias especially the anxiety and conversion types and in anxiety neurosis It is less effective in phobias Compulsive neurotics respond least It may have some value in neurasthenia, but practically none at all in hypochondria Suggestion may be embodied in a word, a prescription a hypodermic injection electricity, or a pious ritual *Hypnosis* is merely a deeper form of the waking rapport of suggestion It is also a substitution neurosis almost an induced hysteria Not everybody is hypnotizable and few patients require hypnosis Given absolute self assurance hypnosis may be induced by restricting the field of conscious attention by means of a mirror a dim light a key or other small object stroking or monotonous verbal soothing Generally it is not necessary to proceed to very deep unconsciousness somnambulism or catatonia Like suggestion hypnotism removes symptoms but does not resolve conflicts It is especially valuable in monosymptomatic hysteria *Persuasion* consists of a conscious appeal to reason and to powerful sentiments In view of the fact that most neuroses are so emotionally toned so unreasonable it is difficult to see how an appeal to reason can be effective nonetheless an impressive therapeutist may try it and be successful in proportion to the amount of suggestion he will unwittingly convey *Reeducation* or *reconditioning* embodying behaviorist principles built around conditioned reflexes are also worth employing

Besides utilizing some of the above therapeutic principles anxiety neurosis can often be relieved by removing specific underlying factors Coitus interruptus should be interdicted undue sexual excitement avoided and dread of pregnancy met by contraceptive teaching Neurasthenics though difficult to manage may be treated with prostatic massage tonics and sedatives and kept out of the hands of quacks More difficult is it to get them to give up masturbation or to restore their potency Hypochondriac symptoms are extremely refractory and the best one can do is to give medication try suggestion and attempt some degree of adjustment to complaints Traumatic hysteria and traumatic neurosis are treated like other neuroses Psychic impotence is best influenced by suggestion and analysis Frigidity in women is a very stubborn condition hysteric anesthesia though refractory is much

less difficult to overcome Both impotence and frigidity are always the cause of marital unhappiness frequently of infidelity and sometimes of divorce Dissolution of marriage is justified where the husband knew of his impotence beforehand Interruption of pregnancy is sometimes indicated when an unwelcome conception precipitates or aggravates a severe neurosis or threatens the onset of a psychosis The same is true of hysteric pernicious vomiting of pregnancy

Psychoanalysis is most useful in the transference neuroses, namely, anxiety hysteria and conversion hysteria phobias and compulsion or obsession neuroses The first two respond best the third fairly well the last not so favorably This is not the place to discuss the theory of psychoanalysis or describe the therapeutic procedure Suffice it to say that in order to practise psychoanalysis one should be well trained in psychiatry and have acquired experience with the method itself A certain amount of judgment and flexibility will obviate the danger of becoming a slave to the method or to rigid technic To be properly analyzed the patient must be fairly intelligent and appreciate the expenditure of time and effort and money necessary for a complete analysis Psychoanalysis differs from all other psychotherapeutic methods in that the patient must learn to accept a new point of view of unconscious psychosexual dynamics It is a question of transference and resistance of dream analysis of neurotic identification with an attachment to the analyst of resolving this transference or substitution neurosis and of sublimation of symptoms and final adjustment of the individual

Obviously only few patients lend themselves to such time consuming treatment—it takes over a year to get results—and not all neuroses are subject to psychoanalytic therapy Nor is it always successful Both the patients and the types of the neuroses therefore require careful selection And while analysis in the hands of an ethical properly trained and intelligent analyst is never harmful it may be wasteful of time and money in unsuitable cases Only very rarely is there danger of precipitating a psychosis but here too a properly qualified analyst knows when to stop or when to begin As the method itself is by no means perfect and the theoretic implications are far from offering an ultimate understanding not to say a solution of the problems of the neuroses it follows that *not even all suitable* cases are cured by analysis In my opinion therefore, there is no good reason for keeping up an analysis for years If one sees no promising results within six months or hopes of a cure within a year, the analysis had better be terminated Not infrequently the method can be modified to suit individual cases Whatever the ultimate judgment on psychoanalysis may be, and particularly as to the efficacy of the method to bring about cures, there can be no doubt of the profound insight into the neuroses it has thus far vouchsafed Nor is there any doubt that many conditions which do not yield to other forms of therapy are resolved by psychoanalysis

I S Wechsler

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VASOMOTOR AND TROPHIC DISORDERS

HEREDITARY TROPHEDEMA

This disease is manifested by chronic edema of one or both legs one or both arms or of the face It may affect but a part of an extremity The condition is hereditary often congenital and extremely

rare In ten years not one was admitted to Bellevue Hospital It affects women more frequently than men and appears in the decade after puberty

The cause is not known The characteristic symptom is a great swelling of the affected parts which either pit but slightly or not at all The skin is much thickened There is no pain or tenderness The discomfort results entirely from the deformity (swelling) This disease is often associated with spina bifida There are transitional forms of the disease which have the characteristics of both angioneurotic edema and trophedema The former condition may precede the latter which becomes its chronic persistent form.

Diagnosis is not difficult Complete or nearly complete absence of pitting upon pressure serves to differentiate the condition from cardiac or renal edema Progressive lipodystrophy is ruled out by absence of the characteristic distribution of fat and by the absence of lipomatous atrophy above the waist line

The prognosis is not favorable No treatment is of advantage The disease is incurable but does not cause death

W M Kraus

CAUSALGIA

Causalgia is a painful condition of the hands or feet which is due to irritation of a nerve by injury Associated with the pain which is characteristically burning in type are glossiness of the skin swelling redness trophic changes of the nails and sweating The slightest stimulus physical or mental, brings a paroxysm of pain The condition was fairly common during the World War I but is rarely seen in civil life

The underlying cause is a disorder of the sympathetic fibers of the injured nerve The disease affects the nerves of the arm in the following order of frequency median ulnar and radial those of the leg as follows internal popliteal external popliteal

Scars and foreign bodies about the nerves should be removed Operations with the object of dividing the sympathetic pain fibers to the affected part are of value in many cases

W M Kraus

ACROPARESTHESIA

Acroparesthesia is a subjective sensory disorder of the fingers which has been known for many years The patients feel tingling and have a sensation of pins and needles or formication in the fingertips The condition is seen not infrequently It occurs almost always in females at puberty or when a true or an artificial menopause occurs Various diseases of the spinal cord have also been found in acroparesthetic patients *e g* tabes dorsalis tumor syphilis multiple sclerosis and syringomyelia Acroparesthesia may be the first symptom of Raynaud s disease It is a disease of the involuntary nervous system which may be due to disease of its centers in the spinal cord or to more general conditions of endocrine origin The disorder is believed to be due to a vasoconstriction of the blood vessels of the distal nerves of the affected extremities Wartenberg attributes the paresthesia to postural compression of the brachial plexus

Symptoms —The condition which is almost always bilateral may begin slowly or suddenly Plunging the hands in icy water may be the immediate cause It is worse during the night and in the morning as a rule In some cases the skin looks blanched. Very slight hypesthesia may be found over the fingertips Pain is rare

The disease is *chronic* but disappears as a rule in later life It does not lead to death It is easily diagnosed either as a symptom or as a disease

The treatment in cases definitely associated with a disorder of the gonads in females should be treated by administering theelin Antuitrin S may also be tried General tonics such as arsenic and iron and faradization of the affected parts are of value in many cases

W M Kraus

MULTIPLE SUBCUTANEOUS GANGRENE

This is a condition closely allied to Raynaud s disease in which multiple areas of gangrene occur It develops in hysterical or neurotic individuals In some cases it is self-inflicted but in others it is definitely of organic origin If the skin is intact over the

subcutaneous gangrene self infliction of the condition can be ruled out

The disease usually occurs in women under forty Frequently a local trauma such as a burn or pricking by a needle has preceded it by months or years Pain and paresthesia often develop before the gangrene The affected areas are of various size and may be anywhere on the skin or mucous membranes They may coalesce The disease may recur frequently or become progressive, spreading widely It sometimes lasts for years but is not fatal The treatment of the organic type is unsatisfactory Psychotherapy should be tried in both the organic and self inflicted types of cases

W M Kraus

PROGRESSIVE FACIAL ATROPHY

This disorder is characterized by wasting of the fat of the face, usually unilateral This is associated with thinning of the skin and depigmentation or abnormal pigmentation The muscles and bones may also be affected The disease is extremely rare

Etiology —The cause is still obscure but is in all probability a disorder of the involuntary nervous fibers in the head region or of the central nervous system The distribution of the disease is certainly that of the sympathetic supply to the head region and not that of any cranial nerve

Symptoms —The disease usually begins before thirty It is found equally in both sexes It may begin about the orbit the cheek or the lower jaw The masticator and tongue muscles may be affected as well as those of the face This involvement does not interfere with muscle function, and there is no reaction of degeneration on electrical testing The eyelashes may fall out or become gray The pigment of the skin becomes either brown yellow or bluish or disappears Pain is often present The atrophy may remain limited to one half of the face but not always Further hemi atrophy of the same type affecting the entire body may occur It is often associated with disorders of the sympathetic system and is closely allied to scleroderma—indeed Cassirer regards it as a form of this disease

This disease may only involve the sub cutaneous fat, and thus resemble progressive lipodystrophy

Diagnosis —The diagnosis is not difficult in clearly defined cases When only pigmentary changes and cutaneous atrophy are present the condition is hard to differentiate from *scleroderma* Cases with loss of subcutaneous fat only are easily differentiated from *progressive lipodystrophy*

Prognosis —The disease as a rule is progressive for a considerable period after it is first observed It then reaches a standstill It does not cause death

Treatment —*There is no beneficial treatment* Removal of the superior cervical ganglion has been attempted

W M Kraus

FACIAL HEMIHYPERTROPHY

This is an extremely rare disorder in which there is unilateral hypertrophy of the skin muscles, and bones of the face This condition may form a part of a generalized hemihypertrophy Some of the cases are congenital others postnatal It is slowly progressive but finally comes to a standstill There is no treatment The diagnosis is best made by x ray of the skull

W M Kraus

PROGRESSIVE LIPODYSTROPHY

This is a disorder of the subcutaneous fat in which there is atrophy above the waist line and hypertrophy below it Relatively few cases have been reported Both men and women are affected The *cause* is unknown

Symptoms —There are no symptoms or signs except the disorder of fat distribution The face is involved as a rule Below the waist line there is accumulation of fat in large masses over the buttocks inguinal regions inner aspects of the knee and the lower legs Pitting is either slight or absent The disease begins usually in the second or third decade and progresses very slowly for a period of years It usually becomes arrested in adult life The condition is not fatal and appears to have no ill-effects

whatsoever One patient seen by the writer passed through a pregnancy quite normally

Diagnosis is not difficult The disease may be confused with the *trophedema of Meige* but the atrophy in the upper parts of the body and the fact that the changes are bilateral are diagnostic

Treatment —No treatment has served to alter the condition

W M KRAUS

MENTAL DISORDERS

(*The Psychoses*)

GENERAL CONSIDERATIONS

THE task of recognizing and characterizing appropriately the different types of psychotic reactions is inevitably complex Some of this complexity is due to uncertainty of knowledge and confusion of thought Since in general more definite knowledge leads to clarification and favors simplification many physicians who have a considerable ignorance about psychiatry may be complacently postponing the necessary study to the time when the complexities may thus be eliminated It seems improbable however, that any highly simplified scheme can be valid or useful because of the inherent complexities of personality functions

Some decades ago when the Kraepelinian nosology ruled it seems to have been generally presumed that the field of clinical psychiatry had been adequately surveyed and plotted into disease entities and that the remaining tasks were the discovery of the corresponding specific pathology and etiology and the development of therapy based thereon A certain measure of success of this type has been brilliantly achieved in two small sectors—in the fever treatment of general paresis and quite recently in the recognition and therapy of certain specific nutritional deficiencies associated with alcoholism Yet, as regards numerically larger groups of psychotic patients those presumptive specific etiologies have not been brought to light by histological biochemical physiological or psychological research It has remained the usual custom in textbooks however to repeat the same old nosologic scheme sometimes varied by substituting other terms—a custom which tends to obscure certain significant changes in psychiatric understanding and practice

The principal modern advances in psychiatric knowledge have been in the direction of a better appreciation of the nature of *integrated personal functioning* and the self induced difficulties involved therein There has been a comparable functional trend in internal medicine aimed at the elucidation of the functional interrelationships of organs and organ systems of tissues and body fluids as they are involved physiologically (*i.e* functionally) in the body s reactions and adjustments to noxious agencies injuries and deficiencies The signs and symptoms brought to light in complaint and by examination are not now viewed by the internist merely as clues to the selection of a diagnostic label they are also utilized as indicators of how the resources of the organism are being employed These findings serve therefore as guides in treatment There is a superficial resemblance to the empirical 'symptomatic treatment of a less enlightened period but the main difference lies in the physiologic strategy by which the clues obtained through clinical reconnaissance and special tests are utilized in care and treatment This functional understanding of disease symptom and treatment in internal medicine has been greatly advanced by the use of new biochemical and physiological technics

In a somewhat comparable way in psychiatry but by different technics there has been a gain in understanding the functioning of the person as a person and a gain in the utilization of such understanding in the strategy of treatment The principal advances have been won by intensive individual biographical case studies and especially by the close scrutiny of patients interpersonal attitudes as these become manifest and modified during study and treatment It is not merely in regard to psychotic patients that the study of interpersonal attitudes has been developed to yield significant facts and insights such attitude-investigation has also great importance for psychoneurotic or psychosomatic conditions and indeed in all phases of medical or surgical practice where the patient as a person has to be specially considered It is

typically through persistent or repetitive patterns of maladjustment in interpersonal relationships that one develops those 'intolerable situations" from which one then recoils into neurotic and psychotic reactions Inadequate or faulty modes of handling the problems of interpersonal relationship produce a large share of the tensions and anxieties which beset every patient in some degree, and in extreme cases seriously upset his physiology and complicate his treatment *Through the study and utilization of patients* interpersonal attitudes one is also able to find or to engender helpful incentives and inner psychotherapeutic resources

A knowledge of the usual course of personality development has special pertinence in the recognition and management of psychiatric conditions because many adult patients revert to, or may never have grown beyond the emotional development of infants, children or adolescents in regard to the manner in which they relate themselves to others and carry on their personal life Special terminologies for the formulation of such emotional fixations or regressions of attitude have been evolved, for example such psychoanalytic terms as narcissistic oral anal urethral phallic genital polymorphous perverse and so on for characterizing zones and stages of erotic interest Less technical sounding terms are probably more generally useful Almost any observer can readily learn to recognize an infantile attitude of expecting infinite service and infinite tolerance from others an attitude of childish irresponsibility and dependence, or an adolescent attitude expressed in gang spirit *hero worship* and 'crushes' a line' of wise cracks and other excesses in adventurous and exhibitionistic activities

In the detailed scrutiny and analysis of disordered personality functioning psychiatrists frequently speak of defense mechanisms or escape mechanisms referring thereby to a variety of unconscious or dimly conscious modes of self deception by which one gains a modicum of self esteem or favorable attention from others By exaggerated distress or by extreme penitence or by ostentatious scrupulosity one may gain in a dependent way from other persons a sort of commiserative favoritism or a mitigation of blame There may be little if any overt behavior in a given situation which an observer would consider blameworthy or in need of mitigation, but even then it is still possible for a person to feel within himself some guilt over suppressed grudges or reactivated resentments, and as a mode of dealing with such a sense of guilt one may resort to propitiatory penitence or distress which seems singularly inappropriate to the overt situation Inwardly censoring and inwardly exculpating reactions may confuse an observer's efforts at understanding Enlightenment may not be readily obtainable from the patient himself, for anyone in emotional situations tends automatically to forget or distort the memory of events having unpleasant implications—as exemplified in almost every traffic altercation In an objective appraisal many of these ego defense reactions seem purely incapacitating or even catastrophic as in suicide or in organ sacrifice via surgery From an adult point of view some of these ego defense mechanisms seem anything but biologically self-defensive They seem biologically futile and senseless Yet every person has lived for a time in a state of infantile and childish dependence when attention seeking and favor inducing behavior constituted his main technic for survival A persistence in or a reversion to such modes of behavior is biologically understandable particularly when one takes into account the social milieu and the possibilities of eliciting favoritism from the social milieu by such 'symptomatology'

Much has been said and written about the emotional determinants of personality disorder or mental illness in a way which may foster the misunderstanding that emotion is pathologic and pathogenic. Emotional experiences are part of normal personality functioning Anxiety and emotion even of a crude and disorganizing sort may serve a biologic function in stirring up reserve resources and forcing needed changes in attitude, and some degree of emotionality is apparently essential in the development and operation of all useful sentiments Unhealthy deviations in personality development arise through the *miscarriage* of emotional functioning *rather than* through emotion Indeed, one may say of all the items of behavior which are observed in

psychotic patients that they are not in themselves specially abnormal for they may also be observed in normal persons the particular psychotic abnormality lies characteristically in the inappropriateness of reaction to the actual situation and in the extraordinary persistence of the patient in maintaining these emotionally distorted misconstructions and *faulty evaluations of* the situation Under good psychiatric study and treatment such distortions will often be found to diminish as more satisfactory interpersonal attitudes are regained or developed

Constitutional and Temperamental Factors.—Constitutional factors are given prominence in the general discussion of psychiatric conditions usually with the implication of hereditary determination through chromosomes Certainly personality functions are strongly influenced by native endowment, but it is hard to say just how Human potentialities are seldom developed to the full whether for good or ill There is considerable evidence of a tendency toward much personality disorder in some families but the interrelated influences of hereditary, social and developmental mechanisms have not been elucidated The best chances for clarification seem to lie in the study of identical twins brought up separately Intellectual capacity, or its converse mental defect, appears in the main to be constitutionally determined Constitutional psychopathic personalities are recognized by one label or another in most clinics but the criteria for such diagnoses and the conceptions of such conditions are not generally agreed upon The diagnostic labels constitutional" or psychopathic form a scrapbasket for a number of types of long term (maybe life long) severe social maladjustments or personal inadequacies So called manic-depressive and schizophrenic psychoses have received a considerable amount of study from the standpoint of heredity but the evidence does not yield unequivocal conclusions A belief in constitutional determinism is a convenient balm to the frustrated therapist

The concepts of constitution and temperament have fostered much psychiatric interest in body build as one of the most obvious indices of individual differences The affective schizophrenic contrast in clinical pictures is paralleled in some measure by a statistical tendency toward *pyknic physique* in those patients with predominantly affective symptomatology and *dysplastic* or *leptosomic physique* in the schizophrenic patients This statistical correlation is of considerable theoretical interest but not sharp enough to have much diagnostic value

Temperament, like constitution, is a tricky term in psychiatric formulations The literature on this topic provides a big catalogue of epithets Endocrinology from which much was expected in the understanding of temperament has not fulfilled those high hopes but it has already brought some specific therapeutic aid in the control of menopausal symptoms and other endocrine disturbances which in certain instances are significant factors in personal maladjustment and even at times in psychotic reactions

As Bleuler has pointed out, it is possible to construct a very elegant conceptual scheme for the formulation of two large groups of psychotic conditions—the manic-depressive and schizophrenic types and certain related disorders—in terms of temperament. This classificatory scheme is based on the postulation of two reaction types the syntonic and the schizoid According to this theory one finds even among normal people a *syntonic* type in which all functions of the personality are characteristically integrated about a definite and relatively vivid affect suitable for the situation of the moment the emotional tone of an experience bringing thought speech gesture autonomic functions and other expressions of the personality into conformity therewith Manic depressive psychosis and chronic depressive and manic moods appear as exaggerations of this normal syntonic reaction type In another group of normal persons those of the *schizoid* reaction type there is a lack of uniformity in the expressions of the personality about a definite affect different and even contrasting strivings coexist Schizophrenic manifestations are interpreted as exaggerations or caricatures of this schizoid type These hypothetical parallelisms between syntonic temperament and manic depressive disorder and between schizoid temperament and schizophrenic disorder

may be employed even in the interpretation of personality disorders resulting from cerebral injuries or intoxications, in which the temperament still shows its influence Bleuler has also assumed that every man has a syntonic and a schizoid component of certain relative strengths determined by heredity Thus one can analyze mixed clinical pictures, and work out discriminating individual prognoses

Clinical Application —Even though one refrains from a rigid faith in constitutional or temperamental determinism clinical experience enforces the recognition that individual persons do show very durable dispositions toward a certain form of reaction The term *personality trend* serves to crystallize in a practically useful way and with appropriate flexibility the general idea that each person shapes up situations or events and reacts to them in a manner which expresses a tendency fairly fixed in his personality Paranoid trends, self-depreciatory and self assertive trends and obsessive and depersonalizing trends are fairly common The expression of these trends becomes extreme in psychotic and neurotic reactions this extreme expression may be moderated, but the underlying trend is not likely to be extirpated from the personality organization This persistence of personality trends can be considered fortunate for society in some ways for such trends in mildly exaggerated forms may constitute the foundation for personal careers of great social value Scholarly and scientific careers might be much less effective without the extreme preoccupation with detail which so often seems to others pedantically obsessive Even paranoid trends may serve in precipitating social reforms and political revolutions The aloof individual with the tendency to shut himself in or withdraw from what is for him a somewhat painful experience of free and easy sociability and with his tendency to depersonalize his impulse life does run grave risks of mental ill health and particularly has a grave handicap in recovering from a mental illness, but he may nevertheless when sufficiently well poised and stable, make a significant social or scientific contribution by developing a new and different point of view and helping thereby to liberate others from the inherent conservatism and stodginess of mere common sense Biographically, it is often possible and useful to trace the development of personality trends first as early modes of reaction in intrafamilial situations, and in other interpersonal situations and then as favored modes of allaying anxiety arising from intrapersonal conflicts A person may thus become more and more disposed to find certain personally predetermined issues whenever tense situations arise

Clinical experience may enable the psychiatrist to recognize frequently recurring *personal issues* about which certain patients are vaguely and indecisively preoccupied He may be able to establish promptly a mutual basis of understanding thereof between himself and the patient which may be of enormous importance for management and therapy Patients also may promptly perceive this recognition of issues sometimes with relief and sometimes with anxiety They frequently misinterpret it as mind reading' and exaggerate its extent

One of the principal differences between the highly skilled and the less skilled psychiatrist lies in the greater ability of the former to sense the nature of the personal issues with which the patient is preoccupied, and in the correlated ability to utilize the patient s own words in clarifying these issues acceptably Conflicting impulses of repentance and resentment or of gratitude and defiance may offer behavioral clues more readily perceived and understood by psychiatrist than by patient particularly by those patients who have a marked syntonic component in their temperament for they tend to throw themselves toward one or the other pole of such issues and so tend to remain unaware of the opposing impulses In a roughly approximate fashion one may say that the patient showing predominantly manic or depressive symptomatology is preoccupied over issues involving respect—self respect and respect to and from others Schizophrenic patients are more typically concerned about affection than about respect. When simple personal affection is brought into question—when one is preoccupied over the lack of this most elementary basis of acceptance by others and feels fundamentally rejected—then the most elemen

tary incentive to social conformity is dissolving The lack of this basic incentive to social living leaves the personality structure prone to dilapidation An awareness of this deep issue may help greatly in the difficult task of establishing tactful contact with schizophrenic patients whose illness is being used as a refuge from potentially bruising *emotional entanglements* In actual practical psychiatric work this sort of diagnosis of personal issues is probably more significant than the diagnosis of formal type of psychosis

Attention to personal issues personality trends temperament and constitution defense mechanisms and emotional immaturity *as shown in the modes of interpersonal relationship*—all such considerations and others of like import, tend to broaden somewhat the borderline between normal and pathologic personality functioning To express it more accurately these considerations enable one to recognize realistically that no sharp line of separation exists and also help one *to give systematic attention to significant* differences between individual patients and to whatever makes a difference Such considerations represent the modern trend to understand and utilize so far as possible the general principles of normal personality functioning in dealing with patients as the *internist utilizes physiologic principles in* clinical evaluation and care

Central Nervous System Factors—Another set of factors of fundamental importance for personality *functioning is* concerned with the *organic soundness* and *physiologic condition* of the central nervous system which is the prime integrating system of the organism An amazing amount of destruction of the brain can in some instances be tolerated without serious psychiatric disorder In general diffuse lesions are more *likely to disturb the personality* The classical example is general paresis (syphilitic meningo encephalitis) victims of *which formerly constituted about 10 per* cent of the admissions to mental hospitals it is now gradually being reduced principally by dealing more effectively with early syphilis Epidemic encephalitis and lead encephalitis are rarer determinants of psychosis Prolonged vitamin deficiencies (often associated with chronic addiction to alcohol) may produce irreversible cerebral damage as in Wernicke s syndrome A large, and increasingly larger number of psychotic conditions *are classified as due to various* types of senile and presenile degenerative changes in the cerebrum, particularly arteriosclerosis The increase is only in part attributable to the increased proportion of aged persons in the population Urbanization and inert economic dependence are statistically important determinants In urban areas about one third of all patients admitted to mental hospitals are more than sixty years of age Many of them show evidences of cerebral damage Lower admission rates in rural areas for these ages are probably to be explained by the greater tolerance for moderately incapacitated persons in farm and village households than in city conditions Probably also some help in preserving a relatively healthier social personality in grandfather' and old Uncle Joe' is provided by the better opportunities in the rural social milieu for some useful and gratifying activities even for those whose brains may be considerably impaired

The *neurologic examination* and the *medical history* provide the most reliable guide to the recognition of all the types of psychotic conditions determined by cerebral lesions Sudden and marked difficulties in *language memory and intellectual* capacity may also be characteristic of cerebral damage Serologic reactions of blood serum and cerebrospinal fluid are of primary diagnostic value *in general paresis It is wise to distinguish*, however the more actively *psychotic* features in the organically disabled patients —*e g* paranoid trends agitated depressive reactions sexual delinquencies or perversions grandiose delusions and so on as distinct from mere incapacitation The crippled personality still has much in common with the same *person s precrippled person*ality and the patient s personal functioning involves as in any other psychosis the psy*chological distortion* of situations by unhealthy interpersonal attitudes and the self defensive and self assertive struggling with such personal issues All this may be aggravated in individually significant ways by the personal meaning of the incapacitation and frustation resulting from the lesions

Fever toxins drugs vitamin deficiencies

dehydration and other noxious influences may produce delirium and other disturbances of personality functions through a temporary impairment of the nervous system although that is not the only way in which illness or incapacitation may elicit mental disorders Some persons can endure incapacitation by illness with more equanimity than others Some even seem to welcome illness as an escape or vacation from something worse Certain operations—e g hysterectomy, hemorrhoidectomy, breast amputation and so on—may involve personal meanings in disturbing ways and so elicit anxious or depressive or paranoid reactions or give such "color" to delirious reactions Preexisting anxieties or unconscious trends may be activated by special examination procedures or treatment measures for example, prostatic massage cystoscopy tube feeding testing for patency of Fallopian tubes, homatropine eye drops and others Obviously a mere medical incident of such kind can scarcely be considered of itself an adequate causal explanation of a psychosis An incident cannot be considered of serious etiologic significance in the individual patient's psychotic reaction without a fair amount of evidence that it is related to vital issues on which the patient has already developed a significant personal vulnerability Interesting examples of the multiplicity of individual factors are encountered in studying postpartum psychoses A brief delirium at such a time may be attributable on the evidence to exhaustion or drugs, but one may have to deal with a special terror of maternal responsibilities or a conflict which hinders the resolution of an old childhood jealousy of baby sister, or an unacknowledged resistance against resuming unacceptable marital relationships, or a panicky way of escape from intimate contact with an obstetrician or nurse toward whom the patient feels shamefully erotic or an autistic delusional intimacy with such a person Speaking rather generally in the psychotic reactions related to acute bodily ills some rough indication of the relative importance of impersonal factors may often be gained from the prominence of delirium or confusion and disorientation in the clinical picture

JOHN C WHITEHORN

STATISTICAL DIAGNOSTIC CLASSIFICATION

For purposes of hospital records and statistical reporting the American Psychiatric Association has agreed upon a classification which has been incorporated into the Standard Nomenclature of Disease, now widely adopted The Standard Nomenclature is codified primarily by topographic and etiologic considerations As far as possible, psychiatric conditions are classified as due to prenatal influence or to infectious or toxic or traumatic causes Other etiologic factors are considered also, such as circulatory disturbances and new growths Psychogenic' and "unknown' etiology are lumped together In large part the classification remains descriptive in terms of clinical pictures or syndromes Naturally the scheme does not succeed in being completely logical In order to be complete and inclusive it subdivides conditions to a rather artificial degree, yet the fundamental psychodynamic considerations have not been explicitly recognized because of the difficulties in codifying the multiplicity of factors that shape one s personal destiny and so contribute to determining the fact and the style of psychotic reaction

In the list given here from the Standard Classification, a parenthetical notation has been added in certain places The percentage figures given only for broad classes and only the more common classes, indicate the relative frequency of the class of disorder noted, expressed as the percentage of the total admissions to representative mental hospitals

Mental Disorders
- *Psychoses due to or associated with infection*
  - Psychoses with syphilis of the central nervous system
    - Meningoencephalitic type (general paresis) (5-10%)
    - Meningovascular type (cerebral syphilis)
    - Psychosis with intracranial gumma
    - Other types
  - Psychoses with tuberculous meningitis
  - Psychoses with meningitis (unspecified)
  - Psychoses with epidemic encephalitis
  - Psychoses with acute chorea (Sydenham s)
  - Psychoses with other infectious disease
  - Postinfectious psychoses
- *Psychoses due to intoxication*
  - Psychoses due to alcohol (5-11%)
    - Pathologic intoxication
    - Delirium tremens
    - Korsakoff s psychosis
    - Acute hallucinosis
    - Other types

Psychoses due to a drug or other exogenous poison
Psychoses due to a metal
Psychoses due to a gas
Psychoses due to opium or a derivative
Psychoses due to another drug
Psychoses due to trauma (Traumatic Psychoses)
Delirium due to trauma
Personality disorders due to trauma
Mental deterioration due to trauma
Other types
Psychoses due to disturbance of circulation
Psychoses with cerebral embolism
Psychoses with cerebral arteriosclerosis (16-32%)
Psychoses with cardiorenal disease
Other types
Psychoses due to convulsive disorder (*Epilepsy*)
Epileptic deterioration
Epileptic clouded states
Other epileptic types
Psychoses due to disturbance of metabolism, growth nutrition or endocrine function
Senile psychoses (1-15%)
Simple deterioration
Presbyophrenic type
Delirious and confused types
Depressed and agitated types
Paranoid types
Presenile sclerosis (Alzheimer's disease)
Involutional psychoses (2%)
Melancholia
Paranoid types
Other types
Psychoses with glandular disorder
Exhaustion delirium
Psychoses with pellagra
Psychoses with other somatic disease
Psychoses due to new growth
Psychoses with intracranial neoplasm
Psychoses with other neoplasm
Psychoses due to unknown or hereditary cause but associated with organic change
Psychoses with multiple sclerosis
Psychoses with paralysis agitans
Psychoses with Huntington's chorea
Psychoses with other disease of the brain or nervous system
Disorders of psychogenic origin or without clearly defined tangible cause or structural change
Manic-depressive psychoses (6-24%)
Manic type
Depressive type
Circular type
Mixed type
Perplexed type
Stuporous type
Other types
Dementia praecox (schizophrenia) (3-35%)
Simple type
Hebephrenic type
Catatonic type
Paranoid type
Other types
Paranoia
Paranoid conditions (2%)
Psychoses with psychopathic personality
Psychoses with mental deficiency
Psychoneuroses (2%)
Hysteria
Anxiety hysteria
Conversion hysteria
Anesthetic type
Paralytic type
Hyperkinetic type
Paresthetic type
Autonomic type
Amnesic type
Mixed hysterical psychoneurosis
Psychasthenia or compulsive states
Obsession
Compulsive tics and spasms
Phobia
Mixed compulsive states
Neurasthenia
Hypochondriasis
Reactive depression (simple situational reaction or other type)
Anxiety state
Anorexia nervosa
Mixed psychoneurosis
Undiagnosed psychoses
Without psychosis (0-15%)
Epilepsy
Alcoholism
Drug addiction
Mental deficiency
Disorders of personality due to epidemic encephalitis
Psychopathic personality
With pathologic sexuality
With pathologic emotionality
With asocial or amoral trends
Mixed types
Other nonpsychotic diseases or conditions
Primary behavior disorders
Simple adult maladjustment
Primary behavior disorders in children
Habit disturbance
Conduct disturbance
Neurotic traits
Mental deficiency (various types and causes)

SPECIAL PSYCHIATRIC CONDITIONS

Many of the psychiatric conditions listed in the Standard Nomenclature do not require special discussion here since they are considered in other sections of this textbook in the discussion of the specific etiologic agent, e g general paresis epidemic encephalitis lead poisoning pellagra and so on Because of the great practical importance of the individual personality in determining modes of reaction it is wise in every case to review the possible pertinence of the *General Considerations* discussed above. Special consideration is necessary, however for a few topics

Alcoholism —About 10 per cent of the admissions to mental hospitals are officially reported as due to alcoholism and another 10 per cent have alcoholism of considerable degree noted as an important contributing cause In addition general hospitals take care of many of the acutely disturbed alcoholics and there are an unknown but large number of persons not yet definitely psychotic and perhaps never going to be psy-

chotic, but who are ruining their careers and undergoing a sort of gradual personality-suicide through addiction to alcohol Of course ethyl alcohol is not the only noxious factor operating in this mass of cases Attempts to escape the distress of personal maladjustments often leads the way in alcoholism and even without alcohol many of these persons would doubtless develop other futile types of defiant dependent relationship Psychiatric assistance aimed at the resolution of inner sources of anxiety and the improvement of personal relationships may in some instances help to free one from the alcohol habit It is usually futile to attempt such treatment without hospitalization for several months Anxiety is dissolved by alcohol more easily than it is resolved by effort and understanding Nonalcoholic sociability is a primary concern in treatment and adjustment

Those interested in vitamin deficiencies have found many instances of pellagra and beriberi among heavy drinkers There is usually a deficiency in several vitamins in varying proportions the commonest lack being in the B group—thiamine, nicotinic acid (niacine) and riboflavin

The clinical pictures resulting from long continued alcoholism are quite variable but may be classified fairly sharply into three types delirium tremens Korsakoff psychosis and so called acute alcoholic hallucinosis

Delirium tremens is an acute illness of a few days duration occurring in chronic heavy drinkers and characterized by marked gross tremor and delirium with vivid hallucinations It is often precipitated by a sudden infectious illness or accident or an attack may be ushered in by a period of restlessness insomnia and anorexia Improved treatment has reduced the death rate markedly, to about 4 per cent Probably many such patients were formerly fatally exhausted by struggling against mechanical restraint and harmed by the administration of whiskey and opiates Rest, vitamins nourishment and tactful management are the main items in treatment Paraldehyde in half ounce doses is helpful in securing rest

Korsakoff Psychosis—After a prolonged attack of delirium tremens the memory may remain impaired or, even without such dramatic onset there may develop in chronic alcoholics (or also apparently, in other thiamine deficient persons) a condition of amnesia disorientation, and confabulation usually with an accompanying peripheral neuritis The condition tends to persist for weeks months or years The prognosis in cases of acute and recent onset has been improved in recent years through the administration of thiamine chloride (up to 200 mg per day) and other nutrients

Acute Alcoholic Hallucinosis Alcoholic Paranoia, and Pathologic Intoxication—In predisposed persons alcoholism may precipitate psychotic preoccupations over sexual problems Commonly there occur hallucinatory accusations of homosexual offenses or of sexual guilt to which the patient reacts more with fear than with depression Other alcoholics of more paranoid trend may make accusations of sexual infidelity against the spouse or express more vaguely a somewhat pointless disgruntlement and suspiciousness It seems probable that these hallucinatory and paranoid reactions of alcoholics are modified examples of schizophrenic disorder In some epileptics or in post traumatic personality disorders or in very unstable persons there may occur episodes of marked excitement and violence after slight alcoholic indulgence followed by amnesia This reaction is called pathologic intoxication

Mental Deficiency—The development of intelligence scales (the Binet and various others) has permitted a quantitative or pseudoquantitative measurement of large population groups from which it is apparent that the intelligence' whatever that may be which is measured by such scales has a unimodal distribution The incidence of feeblemindedness is not a definite quantity but a variable dependent upon the arbitrary selection of the dividing point The limitation of facilities for the care and training of those less well endowed in this respect has tended to overload institutions with just those feebleminded persons whose asocial and troublemaking tendencies cannot be tolerated in the community so that the institutionalized feebleminded are a rather bad lot Included among them are many mentally crippled by antenatal in

juries or anomalies and a few crippled by postnatal injuries to the brain

Much of the work of the world can be done without much intelligence, and many persons of limited intelligence have excellent personal dispositions and never become problems for school courts or psychiatrists A low level of intelligence sets a handicap in the psychiatric treatment of personality disorder when it does occur but so do the self sufficient rationalizations of the intelligentsia Sometimes the person of dull intelligence can be helped more than the bishop or the university professor

It is customary to record mathematically the results of mental tests and to classify degrees of defect thereby the scale consisting of a mental age rating standardized on "normals of comparable experience and opportunity for education Such measurements require that caution must be exercised to insure full cooperation and the absence of serious emotional disturbance or attention disorder at the time of testing as well as a reasonably comparable background of experience and incentive A good report will also state the basal mental age and the scatter, and will note special features of performance as aids to evaluating the person. It is notable that performance tests (*e g* the Kohs block test) may suffer markedly after organic brain injuries in late life while the same patient s vocabulary may remain at a high level Idiots those with the greatest defect have a mental age less than three years or if a child an intelligence quotient less than 20 (Intelligence quotient = 100 × mental age/chronologic age up to sixteen years of chronologic age) Imbeciles rate three to seven years or an IQ of 20 to 49 Morons rate eight years or more or an IQ of 50 or more

It is among the idiots that one finds the well characterized physical abnormalities—microcephaly mongolism cretinism Other special clinical varieties of feeblemindedness are those associated with tuberous sclerosis amaurotic family idiocy progressive lenticular degeneration hydrocephalus diffuse periaxial encephalitis and a recently-discovered metabolic anomaly phenylpyruvicaciduria

Schizophrenic and Affective Disorders — A great number and variety of psychotic reactions occur in early adult and middle life with no convincing evidence or slight evidence of any relationship between the type of disorder and any physical infectious or toxic cause Kraepelin made a magnificent effort to bring clinical order into this heterogenous group Operating ideologically with the concept of disease entities with characteristic course and outcome he found himself obliged in time to set up a considerable series of assumed diseases to accommodate his accumulated case studies but his best remembered contribution was the outstanding dichotomy between the so-called manic-depressive insanity (tending toward recovery and recurrence) and dementia praecox (now frequently called schizophrenia) tending toward a characteristic type of deterioration These two diagnostic terms as now employed cover between them the main bulk of psychoses without clearly defined tangible cause or structural change and together constitute about 35 per cent of admissions to mental hospitals * This sum is fairly consistent within a range of about 10 per cent up or down from year to year from hospital to hospital and in different regions but the separation into manic depressive psychoses and dementia praecox varies enormously Much of the variation is an ideological artefact reflecting different and fluctuating conceptions of what constitutes the condition called dementia praecox or schizophrenia

For example in Dayton s data for 1933 in six of the state hospitals of Massachusetts the sum of these two diagnoses ran for Boston State 27 per cent of new admissions for Danvers 38 per cent for Northampton 42 per cent for Taunton 27 per cent for Westboro 47 per cent for Worcester 24 per cent Yet there was a remarkable variance in the separation into manic depressive psychosis and schizophrenia (or dementia praecox as it is called in official reports) Boston State Hospital reported only 3 per cent as dementia praecox and 24 per cent as manic depressive psychosis, whereas Danvers was reporting almost the

* Involution melancholia, constituting about 2 per cent of first admissions is closely allied to manic-depressive psychosis and paranoid condition also constituting about 2 per cent of first admissions, is closely allied to schizophrenia and to the agitated depressions of the middle period of life.

reverse distribution, 31 per cent dementia praecox and 7 per cent manic depressive psychosis, and Northampton, 35 per cent dementia praecox and 7 per cent manic depressive psychosis There are no special reasons for thinking that there is any real difference corresponding to these differences in classification There is some reason to think that the deteriorated areas in large cities contribute unduly large numbers of dementia praecox cases but if this were happening in Boston in 1933 it should have changed the statistics in the opposite direction

It is probable that those responsible for the diagnostic classification at Danvers and Northampton were interpreting rather *strictly the criteria for a manic* depressive diagnosis and that the criteria for dementia praecox were being strictly interpreted at Boston State Hospital Comparable strictness for each group would leave the greater number of the cases (some 12 per cent to 35 per cent of all first admissions) as of undetermined diagnosis

Another view is that we deal here not with two distinct diseases or more, but with two somewhat contrasting reaction tendencies often simultaneously at work in the same patient the relative strength of these tendencies determining the preponderance of trend in the specific illness of a specific patient This method of dividing the case material splits it in three groups (1) preponderantly manic depressive types of reaction, (2) preponderantly schizophrenic types of reaction and (3) about equally balanced schizo affective or mixed types of reaction This seems to the writer the most reasonable view *and it is also his opinion* that the mixed or intermediate types outnumber the extreme types on first admissions and later become more clearly schizophrenic" or 'affective or without psychosis depending in part upon the working out of inner predetermined personality dynamics (which might theoretically be early recognized and their outcome predicted) but in part also upon unpredictable events including the quality of psychiatric treatment received The whole matter of differential diagnosis' in this field is more significantly an individual affair of personality dynamics personality structure *and* specific situation than it is one of specific ' disease or fixed 'reaction pattern" (See General Considerations) Probably space should be left in the diagnostic scheme for a few cases of 'true manic depressive psychosis" and "true dementia praecox' just as there is a space for ' true *paranoia"—just to have some nouns* to give substance to the useful adjectival terms, 'affective" and ' schizophrenic" tendencies This point of view can be reconciled with the use of the *Standard Nomenclature* by regarding these two main divisions and their numerous subheadings as merely cross sectional descriptions of phases in a potentially variable clinical *course*

There is in the state hospitals a vast and increasing accumulation of patients showing *mainly* schizophrenic tendencies, and there are excellent recovery rates for those showing mainly affective tendencies The practical importance of the results of these trends may be exemplified by the fact that nearly one quarter of all hospital beds in existence are used for schizophrenic patients Since recovery is much more probable in *the first year of illness than thereafter,* many state hospitals now have admission services to focus their best therapeutic resources and efforts on those newly admitted Some alarm has been expressed lest the human race be swamped by a rising tide of schizophrenia, but the most careful studies indicate that the incidence is not increasing

Kraepelin saw the unifying clinical principle of the dementia praecox group in an assumed uniformity of outcome in a characteristic deterioration with lack of emotional responsiveness and looked for evidences of some endogenous intoxication *Many abnormalities of an* anatomic or physiologic sort have been found—dysplastic build low basal metabolic rate low glucose tolerance *subnormal body temperature* slow circulation time impaired homeostasis and so on but these abnormalities do not statistically combine to separate out *a clear* physiologically characterized group Some have one abnormality some another and with little if any relation to the clinical picture *Rather it seems* that the candidates for schizophrenia are drawn in a significantly large proportion from among the *biologically* handicapped and the biological handicaps may be of the most diverse sort There are also some persons having schizophrenic re-

actions who seem to be fine anatomic and physiologic specimens

Bleuler, in proposing the term "schizophrenia" proposed also what he considered a more apt descriptive characterization of the primary unifying abnormality of this group—a rupture or loosening of associations (presumably by reason of neurohistologic lesions although this was later attributed by him to the schizoid temperament) The detailed features of the clinical picture were considered as brought about in a psychologic manner in the association loosened brain Perhaps the most striking and significant feature pointed out by Bleuler *in schizophrenia was ambivalence—coexistence* of contrary feelings toward the same person and the patient's awareness of these contrary feelings Perhaps all persons have some degree of ambivalence toward the more significant figures in their lives but most people are seldom aware of it feeling in general all one way at one time and all another way at another time The schizophrenic seems therefore not bound together in the same univalent (perhaps artificially univalent) emotional experience that "makes sense to the ordinary person The appearance of disorganization and disintegration is heightened by the occurrence of absurd behavior and bizarre delusions and hallucinations Indeed the very occurrence of delusions and hallucinations in the presence of good orientation seems absurd and bizarre The apparently disintegrated schizophrenic may however be highly integrated in his own peculiar way and inwardly consistent

The 'shut in' type of preschizophrenic personality was pointed out by Hoch and Meyer and Meyer postulated that bad mental habits might lead to the dementia praecox type of behavior a concept later expressed by the term parergasia"

Considered as phases in the dynamic functional adjustment to life the different styles of schizophrenic reaction can be partially understood as tentative attempts to reach a psychotic adjustment in life through accepting passive dependence not usually in a frank and outspoken way but by way of delusional distortions and disparagements which may give to the ultimate dependence an air of independence Some attain such I don't care anyway' adjustments as the Empress in prison or silly idolatry, or offensively punctilious obedience To reach such an adjustment is not easy for most of those who try that route into passivity and in the writer's opinion most of the more active schizophrenic symptomatology represents the antischizophrenic struggling so to speak, of the patient's own more active normal impulses and feelings of obligation

The formulation of the conditions called "manic depressive psychosis or allied disorders (affective disorders) has suffered much distortion from the very natural tendency of writers to set up somewhat artificial *dichotomies and antitheses Neat diagrams* portray (and exaggerate) the antithesis between elated and depressed moods Tradition sets up a contrast between these affective disorders and schizophrenia. Actually the schizophrenic and affective types of patients have more resemblances than differences There are no pathognomonic signs for one or the other condition Both groups show prepsychotic trends toward moodiness and seclusiveness Indeed one may say that any psychotic patient is somewhat schizophrenic—a bit cracked" or crazed"—terms which have the same primitive meaning as schizo phrenia' So too there is much empirical justification for the old fashioned view which set melancholia as a sort of common denominator of all psychotic reactions for most psychotic patients do have decidedly melancholy period at some time.

One of the grave dangers in the schizophrenic and affective types of reaction is the risk of suicide To prevent suicide close supervision may be needed but nagging reminders should be avoided Trained personnel and systematic routine can unobtrusively avoid many of the risks Risks may have to be taken at times to maintain reasonable opportunities for activity and recovery but it is wise to share the responsibility of such decisions with responsible relatives Two sources of error in practical judgment about affective disorders are so common and so serious as to call for special warning First, the shift from a depressed to a manic phase does not eliminate the danger of suicide it may increase that danger Second violent crimes against others

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complacently convinced of his or her transcendent importance Commonly there are also hallucinations concordant with the delusions but the hallucinations may be long delayed in their appearance The more intelligent among the paranoid schizophrenics are likely to evolve elaborate systematized delusions of persecution or grandeur, or both (This diagnostic group shades off gradually through a less definitely schizophrenic group called *paranoid condition* toward a very rare and rather idealized diagnosis of *true paranoia* meaning without deterioration or hallucinations)

SIMPLE —The patient without much delusional or hallucinatory embroidery to the theme of his or her preoccupations insidiously loses interest in an active career and drifts into irresponsible vagrancy prostitution or hospitalized inertia

Personal Diagnostic Formulation.—The psychiatric diagnosis for statistical purposes in terms of the Standard Classification is seldom if ever adequate for the purpose of guiding care and treatment because a due regard for personalities and situations requires a more specific consideration of personal attitudes and their pertinence For these purposes it has become the custom in many psychiatric clinics to work out for each patient a personal diagnostic summary No uniform system has yet become standard Of several plans which have been found useful by the author the following outline is the one which includes the most definite suggestions

A *Organic Lesions Toxic Effects in the Central Nervous System and Other Somatic Factors*
(Give a brief summary of *deficits disabilities* and *handicaps* due to any of these three classes of causes as justified by clinical and laboratory evidence)

1 BRAIN LESIONS
(State nature, location extent and cause)

2 TOXIC FACTORS
(Include broadly any and all significant harmful effects from infections drugs, poisons alcohol exhaustion metabolic and endocrine disorders vitamin deficiencies uremia, anemia, momentary circulatory or respiratory failure starvation dehydration etc., which on the evidence seem to be exerting a deleterious influence on the central nervous system)

3 OTHER SOMATIC DISEASE, ACUTE OR CHRONIC
(How does it limit or hinder the person?)

B *The Personality*

1 THE CLINICAL PICTURE OR PATTERN OF PRESENT PERSONAL REACTION

(a) Adjectival Characterization
(A brief characterization as delirious confused amnesic panicky hypomanic, manic, agitated-depressive retarded-depressive anxious neurasthenic, obsessive catatonic hebephrenic paranoid hypochondriacal dissociative asocial self blaming self praising etc., or combinations thereof N.B *Destructive trends* whether suicidal, homicidal assaultive, mutilative or surgery seeking should be specially noted and evaluated, and *underlined*)

(b) Sentiment-Organization Now Dominant
(In what patterns of personal relationship does the patient now bring about, or permit, personal contact and relationship with others?)

2 BIOGRAPHICALLY ESTABLISHED CHARACTERIZATION of the patient's constitutional and temperamental assets and liabilities, personality trends and special emotional needs and vulnerabilities as developed in familial setting and exhibited in pre-psychotic life

3 ANALYSIS OF CURRENT PERSONAL ISSUE AND LIFE SITUATION

(a) The "complaint *problem*" and the patient's *attitudes* about the complaint about the life-situation and about the responsibilities involved

(b) The potential *advantages* and *disadvantages* in the present life-situation *for* the satisfaction of the patient's *emotional needs* by the type of reaction shown

4 ALTERNATIVE POSSIBILITIES by which *this* patient may resolve *this* situation more satisfactorily for *this patient's needs* with due consideration for the welfare of others

JOHN C WHITEHORN

PSYCHIATRIC THERAPY

The personal diagnostic formulation is designed primarily to provide a grasp of the considerations necessary to guide the therapy It is of primary importance to provide appropriate surgical and medical measures for conditions remediable thereby

Medical Treatment —*Placebo medication* has a legitimate diagnostic purpose but the use of placebos as a regular therapy is of dubious propriety and is unjustified when good psychotherapy is available Generous provision of vitamins is empirically and rationally justified even when no specific deficiency state is clinically demonstrable Sex hormone treatment if utilized should be cautiously integrated into the general therapeutic strategy lest conflicts be unduly aggravated

Sedative and *hypnotic medication* is widely (too widely) and intensively (too

are more commonly committed by depressed than by manic patients These practical points are also of much theoretical interest as indicating needed corrections to oversimplified formulations

As psychobiological modes of reaction the manic and depressive phases are in our culture expressive of more conventional patterns of personality integration than are the schizophrenic tendencies These patients are quite likely to have established some consistent loyalties and also to have harbored submerged resentments and frustrated ambitions without insight into this ambivalence The manic reactions may represent a sort of 'generalized rehearsal with triumph" of an opportunity previously lost through failure of self assertion The precipitating situation may be found on close scrutiny, to have seemed to offer a startling success *if only* one seized it with supreme confidence The manic assertiveness is not to be construed as a practical striving toward a particular success but as a kind of generalized demonstration of adequacy not quite convincing to the patient himself It is much more difficult to formulate a generalized functional significance in the great diversity of depressive reactions There is the common paradox of the self derogatory or self-accusatory patient who shows an amazing resistance to advice or guidance from others Some of these depressed patients seem to be driven by a sense of guilt to absurdly extreme self accusation and yet to be inwardly blocked by some self justifying resentment from that very relief which they seek through overdone repentance Other depressed patients seem more simply defeated for a time through lack of self confidence

Appropriate descriptive terms may be very briefly defined as follows

In the *retarded depressive* type or phase of reaction the patient who has been growing increasingly indecisive and feeling inadequate complains of inability to carry through any task and becomes extremely slow and groping in response

In the *agitated depressive* type or phase of reaction the patient appears harried and perplexed paces about wrings hands mutters and laments in lugubrious but insistent voice *frequently talks* in a self accusatory or self derogatory way but vaguely implies misunderstanding or *self justification* and sometimes hints at or expresses definitely paranoid delusions of persecution (Symptomatically this condition shades in one direction into that called involution melancholia in which there may be more marked somatic delusions and a more marked routinization of complaint and in the other direction into paranoid condition')

In these depressive states physiologic rhythms and functions are commonly altered Constipation is practically universal sleep is broken and the early morning *is likely to be a period of special distress* Women become indifferent or antagonistic to sex and men become impotent, appetite for food diminishes and troublesome food delusions may be expressed

In the *manic* phase of reaction the patient appears elated (or, more accurately inflated) in mood rushes with apparent assurance from one thought or action to another overflows with suggestions, criticisms and advice and is demanding and assertive toward others The underlying uneasiness and self distrust which bear witness to preoccupations identical with those of the depressed patient are only manifested in irritability, in a quickness in sensing slights and in momentary lapses into tears or dejection *Hypomanic* means mildly manic

A '*benign stupor* has been described as part of the manic depressive picture but it usually turns out to be not so benign—a tentative step toward the schizophrenic style of psychotic dependence

In *clinical symptomatology* the *schizophrenic* patient is likely to appear in one of four types of clinical picture

HEBEPHRENIC—The patient appears silly childish giggling or ecstatic *frequently* carrying on hallucinatory conversations with apparent pleasure or amusement

CATATONIC—The patient appears tense stiff manneristic antagonistic or absurdly obedient subject to long periods of motionless rigidity or outbreaks of apparently aimless excitement and activity

PARANOID—The patient appears suspicious or frightened about threatened danger or accusation or concerned about some impending greatness or special mission or

same time these hospital situations may be utilized for the mutual gain in insight of the patient and his personal associates

The Psychiatrist —The personal role of the psychiatrist and of his special nursing, social and occupational aides, in the treatment of the psychoses has been the subject of numerous special treatises which should be consulted for detailed guidance and frequent review Like all other arts psychotherapy is hard to learn from books To a certain extent it can be the subject of scientific investigation and report, but psychotherapy which has been systematized and learned by rote is likely to become excessively rationalistic and ritualistic, and fails to meet many patients' needs It also tends to shift certain susceptible patients towards an obsessive or compulsive type of neurotic adjustment.

Many patients lack *incentive to normal living* In a certain sense the psychiatrist may be said to function as a sort of ambassador between the practical common sense world and the alienated patient In the main, it is through reliability considerateness, and his special acquaintance with human problems and his skill in recognizing them that the psychiatrist assists the patient toward a more effective and gratifying personal reorientation of attitudes He seeks to aid the patient both in the better understanding of personal issues and situations, *and in the more spontaneous participation* in life

Whereas the neurotic patient may, in general in this analytic process be prepared to gain much through a fairly direct analysis of his personal attitudes it is usually better with the psychotic patient to *begin* such efforts in terms of an analysis of *situations* often most usefully the trivial situations of the moment rather than the more vital ones which the patient is likely to face only with a protective rigidity A very valuable therapeutic ability is that of perceiving the *larger issues within the trivial incidents* and of dealing with them by a kind of *double entendre* This is the main constituent of the psychiatrist's so-called intuition'

JOHN C WHITEHORN

intensively) employed in the management of restless and disturbed patients This practice is more common in general hospitals, outpatient departments and private practice than in psychiatric institutions where better organized work and recreation, warm baths and wet packs, under well trained supervision, provide more adequate and less harmful relief For the stuporous restlessness of acute exhaustion states seen in war conditions or other prolonged emergencies a special regimen of a few days of barbiturate narcosis has been found very helpful combined with generous fluids and nourishment, followed when necessary by prompt and vigorous explanation and encouragement

Amphetamine sulfate (*Benzedrine*) which came into clinical use for the treatment of narcolepsy has been found useful in overcoming mild depression Its use may precipitate paranoid reactions, or increase the agitation in agitated depressions

In recent years several types of *shock treatment* for psychotic conditions have received extensive trial hypoglycemic shock induced by insulin and epileptiform convulsions induced by metrazol or other drugs or by faradic electrical stimulation applied to the forehead Sudden and dramatic improvement in behavior or recovery from psychosis may be thereby induced in a considerable percentage of patients but the psychosis may recur Deaths from such forms of treatment are rare Postmortem examinations show in some cases diffuse cerebral injuries Fractures especially compression fractures of the bodies of vertebrae, were common in earlier procedures but have become rare with improved technic of administration Curare has been used to 'soften the convulsion The earlier shock treatments were given to schizophrenic patients who were thought to be otherwise unlikely to recover More recently the enthusiasm has shifted to the use of electro shock in depressed patients to shorten the illness It is not known by what mechanisms the shock experience may induce improvement when it occurs Final evaluations must be based on more prolonged case studies than there has yet been time to report

Surgery—There may be special psychiatric indications for surgery The surgical removal of a pulmonary abscess for example, may be good mental hygiene in certain cases for this removes an olfactory barrier to social adjustment, but plastic facial surgery or the operative correction of strabismus or other quasicosmetic surgical procedures should not be used for psychotherapeutic effect without good psychiatric teamwork to deal with the potentialities of severe anxiety reactions or paranoid developments in case the operation does not bring the desired ' popularity " Unnecessary appendectomies or exploratory operations or sham operations are not usually psychotherapeutically effective for the relief of psychiatric conditions and when tried for that purpose commonly create more trouble and enormously increase the difficulties of subsequent attempts at therapy *Leucotomy* of the frontal lobes may relieve anxiety in chronic agitated patients and the sacrifice of some measure of intelligence judgment and self control may not be too high a price to pay for this possibility of relief Eugenic considerations may justify *sterilization* In regard to sterilization as also in regard to abortion for the prevention of a psychosis it is necessary to get the concurring judgment of colleagues, and one must consider prevailing sentiments and laws Special sensitivity or emotional vulnerability such, for example as may be involved in gynecologic rectal or breast operations, may lead one to delay the operation if delay is permissible until the patient s attitude about it has been clarified or fortified

Institutional Care.—Among the more specialized psychiatric procedures *resident institutional care* is very important Protective custody of this sort may be made necessary by destructive trends in the patient, or to avoid the effect of extravagant or dangerous errors of judgment Institutional care may help greatly by providing a simplified yet active regime free from the fretting responsibilities, advice and importunities of family friends and work associates A well organized institution provides rest but it also provides appropriate and graduated work recreation and less demanding personal relationships There is usually enough variety or flexibility in hospital situations so that they can be adjusted to the changing needs of the patient and to his increasing responsibility in convalescence and at the

	mg./100 ml.
Phosphorus, inorganic, serum, adults	3-4
children	5
lipoid serum	12-14
total acid soluble serum	18-25
total serum	35-45
Potassium, blood	1.0-2.0
serum (4.1-5.6 milliequiv. per liter)	16-22
Protein total serum	6.0-8.2%
Prothrombin concentration (Warner Brinkhous and Smith)	70-100%
(Quick)	50-100%
Prothrombin time (Quick)	12-16 sec.
Sodium, blood	200
serum (139-152 milliequiv. per liter)	315-340
Solids, total	19-23%
Sugar (glucose) blood	70-110
Sulfates as SO_4 ethereal serum	2-3
inorganic, blood	1.8-3.0
serum	0.9-1.5
total, serum	3-4.5
Urea, blood	15-30
Urea nitrogen blood	8-15
Uric acid blood	2-4.5
Vitamin C (reduced ascorbic acid)	0.7-1.2
Water content	77-81%

CLINICAL EXAMINATIONS

Bleeding time		1-3 min.
Cells, Differential count.		
Lymphocytes	1250-3500 per cu. mm.	25-35%
Monocytes	200-1000 per cu. mm.	4-10%
Neutrophils		
Young (non filament)	150-1500 per cu. mm.	3-15%
Adult (filament)	2500-6000 per cu. mm.	50-65%
Eosinophils	25-400 per cu. mm.	0.5-4%
Basophils	0-200 per cu. mm.	0-2%
Erythrocytes	per cu. mm.	4.2-5.5 million
Leukocytes	per cu. mm.	5-10 thousand
Platelets	per cu. mm.	200-500 thousand
Reticulocytes	per cu. mm.	0.5-2.0% red cells
Clot retraction time		1-3 hrs.
Coagulation time, capillary blood		3-6 min.
venous blood		5-20 min.
Congo red test. Disappearance in 1 hr. of less than 40% dye from the blood and no dye in urine		
Erythrocyte diameter average		7.5 microns
"Fragility" of erythrocytes maximal resistance		0.32% NaCl
minimal resistance		0.42% NaCl
Hematocrit (vol. % of cells)		42-50%
Hemoglobin adults females	Gm. per 100 ml	12.8-15.2
males	Gm. per 100 ml	14-17
children varies with age	Gm. per 100 ml	10-18
Icterus index		4-6
Indexes of erythrocytes color saturation volume		0.9-1.1
Sedimentation rate Cutler men		2-8
women		2-10
Rourke & Ernstene	not more than	0.4 mm. per min.
Westergren	less than	20 mm. per hr.
Wintrob men		0-9 mm. per hr.
women		0-20 mm. per hr.
Viscosity blood		1.4 to 1.6
Volume, blood	per Kg. body weight	70-100 ml
	per sq. meter body surface	2800-3800 ml

FUNCTIONAL TESTS

Bromsulfalein	No dye remaining in serum 20 min. after injecting 2 mg. per Kg. body weight
Or	No dye remaining in serum 45 min. after injecting 5 mg. per Kg. body weight.
Cephalin flocculation	No precipitate
Concentration and dilution	Sp. gr. of urine after dry day 1.025 or more; after water day 1.003 or less.
Creatin tolerance	70% ingested creatin retained in adults

NORMAL VALUES FOR CLINICAL EXAMINATIONS

With the constant multiplication of clinical examinations, the results of which are expressed in figures it becomes increasingly difficult for the clinician to keep in his memory the values that are to be expected in the normal person It seemed worth while therefore, to assemble for ready reference some of the figures commonly regarded as being within normal limits No apology is made for using 'normal' in this connection

BLOOD

CHEMICAL CONSTITUENTS

(Values are given in mg per 100 ml [1 dl 100 cc.] unless otherwise stated)

		mg/100 ml
Acetone and aceto-acetic acid		0.3–2.0
Acetone bodies total		0.8–5.5
Albumin serum		4.6–6.7%
Albumin globulin ratio serum		1.5:1 to 3:1
Amino acid nitrogen blood		5–8
Amylase serum		80–150 mg glucose liberated from starch by 100 ml blood serum
Ascorbic acid reduced plasma		0.7–1.2
Base, total serum		145–160 ml N/10 base per 100 ml serum
Bilirubin		0.1–0.5
Bromine		0.2–0.6
Calcium serum (4.5–5.5 milliequiv per liter)		9–11
CO_2 combining power plasma, adults (44–52 milliequiv per liter)		55–75 vols %
children		45–65 vols %
CO content plasma arterial		45–55 vols %
venous		50–60 vols %
Chlorides as NaCl blood		450–500
plasma		570–620
serum (99–110 milliequiv per liter)		350–390
Cholesterol blood		150–230
plasma		160–200
Cholesterol esters plasma		100–150
Creatin		3–7
Creatinine blood		1–2
Fatty acids blood		290–420
Fibrinogen plasma, as fibrin		200–600
Globulin serum		1.2–2.3%
Glucose blood		70–110
Iodine total		0.004–0.01
Iron blood		45–55
serum		0.04–0.23
Lactic acid		5–20
Lecithin		200–250
Lipase serum		0.2–1.5 ml N/20 NaOH per ml serum
Lipoids total plasma		500–550
Magnesium blood		1.6
serum (1.6–2.5 milliequiv per liter)		2–3
Nitrogen nonprotein blood		15–40
total		3.0–3.7%
undetermined		4–18
urea blood		8–15
Oxygen capacity blood		18–24%
Oxygen content arterial		15–23%
venous		10–18%
pH arterial		7.3–7.35
venous		7.2–7.25
Phosphatase acid		3–4 units
alkaline, adults	(Bodansky)	1.5–4 units
	(King and Armstrong)	14 units
children	(Bodansky)	5–15 units

Gastric test meal, free acid	24–45 degrees (ml N/10 alkali per 100 ml gastric fluid)
total acidity	50–100 degrees
volume	5–150 ml fasting
	40–50 ml 1 hr after Ewald meal
Kidney threshold for glucose	160–180 mg per 100 ml blood
P R interval in electrocardiogram	0 1–0.2 sec
Q-R-S time in electrocardiogram	0 1 sec.
Respiratory quotient, for burning carbohydrate	1.00
fat	0 71
protein	0 80
under basal conditions	0.83
Venous pressure, peripheral vein	60–120 mm water
Vital capacity	3500–4,00 ml

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Galactose tolerance	Excretion of not more than 3 0 Gm galactose in the urine in 5 hr after the ingestion of 40 Gm galactose
Glucose tolerance	Standard After ingestion 100 Gm glucose or 1 75 Gm glucose per Kg body weight, blood sugar not more than 180 mg per 100 ml after ½ hr and return to normal in 2 hr Sugar not present in all urine specimens.
	Exton ½ hr blood sugar not more than 75 mg per 100 ml higher than the fasting sugar and 1 hr blood sugar not more than 30 mg higher than in the ½ hr specimen
Hippuric acid	Excretion of 3 0-3.5 Gm hippuric acid in urine in 4 hr after the ingestion of 6 0 Gm sodium benzoate
Or	Excretion of 0 70 Gm hippuric acid in urine in 1 hr after the intravenous injection of 1 77 Gm sodium benzoate.
Phenolsulfonephthalein	Intramuscular injection 40–60% in urine in 1 hr 55–75% in urine in 2 hr
	Intravenous injection 25% or more in urine in 15 min
Prothrombin test of liver function	Increase of 15% or more in the prothrombin concentration in the blood in 24–48 hr after the injection of synthetic vitamin K
Urea clearance	40 ml *or more blood cleared per minute 75–125% of average normal.*

URINE

Acidity titrable	200–500 ml N/10 alkali
Amino nitrogen	0 4–1 0 Gm per 24 hr
Ammonia as NH_3	0.5–0 6 " "
Calcium	0 1–0 7 " "
Chlorides as NaCl	10–15 "
Creatinine	1.0–1 6 "
Glucose	0.5–1.0 " "
Nitrogen total	12–18 " " " "
Phosphates as P_2O_5	2 0 " " " "
Solids total	55–60 " " "
Sulfates as SO_3	1.8–3.0 " "
Urea	20–35 " " "
Uric acid	0 4–1 0 " "
Urobilin	up to 1 20 dilution
Urobilinogen	less than 4 mg per 100 ml

CEREBROSPINAL FLUID

Cells	fewer than 10 per cu mm., all lymphocytes
Chlorides as NaCl	720–750 mg per 100 ml
Colloidal gold test	not more than one in any tube
Glucose	45–65 mg per 100 ml
Protein	15–40 mg per 100 ml
Pressure	100–200 mm water

MISCELLANEOUS

Basal metabolic rate — minus 10% to plus 10%; 40 calories per sq meter per hr; 1800 calories per day

Circulation time

		Average	*Range*
Alpha lobeline	arm to carotid sinus	*8 5 sec*	5–12.5 sec
Calcium chloride	arm to tongue		9–15 sec.
Calcium gluconate	arm to tongue	12.5 sec.	10–16 sec.
Carbon dioxide	lung to carotid sinus	15 6 sec.	9–21 sec.
Decholin (sodium dehydrocholate)	arm to tongue	10 sec.	8–14 sec.
Ether	arm to lung	5.5 sec	3.5–8 sec.
Fluorescein	arm to eye	12 sec	7–15 6 sec
Histamine	arm to carotid sinus	18 sec	13–30 sec
Macosol (Mg sulfate, Ca gluconate and Cu sulfate)	arm to foot	32 sec.	20–40 sec
	arm to hand	23 6 sec	
	arm to perineum	21.2 sec	15–29 sec.
	arm to tongue	13 7 sec	5–24 sec.
Magnesium sulfate	arm to tongue	13 7 sec	10–19 sec.
Saccharin	arm to tongue	12 sec.	9–16 sec.
in children		8 6 sec.	5–13.5 sec.
Sodium cyanide	arm to carotid sinus	7 sec.	5–10 sec.

in the treatment of superficial wound infections and surface burns of limited extent

Administration.—For multiple intravenous or intramuscular injections the most convenient solution is one containing 5000 units per cc of sterile physiologic salt solution, but more dilute solutions may be used when indicated When a constant intravenous infusion is used a solution containing 25 to 50 units per cc of sterile saline or 5 per cent glucose solution is usually employed Solutions for injection into the various body cavities are ordinarily made up to a strength of 1000 units per cc of saline solution For topical application in the treatment of burns and superficial infections saline solutions with a concentration of 250 to 500 units per cc are satisfactory

Action.—The action of penicillin in clinical infections appears to be bacteriostatic rather than bactericidal so that it is essential to continue treatment until the infection is definitely controlled or eradicated Not infrequently relapses occur when treatment is discontinued too soon after the first signs of improvement have appeared

The antibacterial action of penicillin is selective It is very active against certain species and almost totally without action against others those susceptible are chiefly gram positive species Except for the gonococcus and the meningococcus gram negative bacteria are not significantly inhibited by it

The following list includes the more important pathogens that have been found to be sensitive to the action of penicillin

Gonococcus	*Streptococcus viridans* (most strains)
Meningococcus	*Clostridium tetani*
Hemolytic streptococcus	*Clostridium welchii*
Pneumococcus	*Corynebacterium diphtheriae*
Staphylococcus	*Actinomyces bovis*
Nonhemolytic streptococci (most strains)	*Treponema pallidum*

Occasional strains of susceptible bacteria are encountered that are resistant to the action of penicillin Likewise in a few cases susceptible organisms have been observed to develop resistance to penicillin during the treatment of clinical infections

The following list includes some of the more important pathogens that have been found to be insensitive to the action of penicillin It can be seen that it has no effect against the whole group of gram negative bacilli

Enterococcus	*Vibrio cholerae*
Escherichia coli	*Bacillus proteus*
Bacillus typhosus	*Pseudomonas aeruginosa*
Bacillus paratyphosus	Friedlander s bacillus
Bacillus dysenteriae	Brucella group
Hemophilus influenzae	*Mycobacterium tuberculosis*
Hemophilus pertussis	*Pasteurella pestis*
Hemophilus ducreyi	*Pasteurella tularensis*
	Yeasts
	Molds

Preliminary studies have indicated that penicillin has no effective action against rickettsiae or the viruses

Indications.—While the full range of penicillin s usefulness remains to be determined clinical experience has already established the fact that it is the best therapeutic agent available for the treatment of several important groups of infections These are

All staphylococcic infections with or without bacteremia respond better to penicillin than to any other chemotherapeutic agent More than 500 cases of staphylococcic bacteremia have been treated with penicillin with 80 per cent of the patients surviving—a low mortality rate that no other form of therapy in this disease has ever achieved Of the patients with acute osteomyelitis who have been treated 90 per cent have recovered Of patients with lateral or cavernous sinus thrombosis recovery has taken place in 75 per cent

In serious localized staphylococcic infections without bacteremia improvement or recovery has occurred in more than 80 per cent of cases It should be emphasized that in this type of infection prolonged and intensive treatment is usually necessary and that recurrence of the active infection after a period of latency must be guarded against

Frequently adequate surgical management as well as the use of penicillin is nec

TREATMENT OF INFECTIONS WITH PENICILLIN*

Penicillin was discovered in 1928 by Dr Alexander Fleming who showed that filtrates of the culture liquor of the mold *Penicillium notatum* exert a potent antibacterial action on a number of bacterial species The application of Fleming s important discovery to the problem of the treatment of infections was postponed for more than a decade until Florey and his colleagues demonstrated that stable nontoxic preparations of penicillin could be produced in sufficient quantity to permit the effective treatment of infections in man The value of *penicillin as a therapeutic agent in a wide* variety of infections has now been well established by extensive clinical investigations both in England and in the United States

Penicillin possesses certain advantages that render it definitely superior to the sulfonamides Against susceptible organisms its antibacterial action is many times more potent than that of the sulfonamides At the same time even when it is administered in full therapeutic doses penicillin is entirely free of significant toxicity for the host Unlike the sulfonamides it is not inhibited by pus or the breakdown products of tissue autolysis

Description —Penicillin itself is an unstable acid For clinical use various salts of the acid are employed the sodium salt being the preparation that has been most extensively studied Recent work has indicated that the calcium salt which is less hygroscopic and somewhat more stable than the sodium salt does not differ from the latter either in effectiveness or in toxicity

The salts of penicillin are readily soluble in physiologic salt solution distilled water and 5 per cent glucose solution Since solutions of penicillin are less stable than the dried powder they should be freshly prepared every twenty four or forty eight hours Both the solutions and the dried powder may become inactivated by exposure to room temperatures for prolonged periods, hence to avoid deterioration they should be stored at a temperature below 10° C

The exact chemical structure of penicillin is not yet known, and the drug has not been prepared synthetically The preparations in use today are still obtained by extraction from the culture liquor in which *Penicillium notatum* has been grown The extracts that were first employed clinically had a very low potency and the final preparations contained 85 to 90 per cent of impurities, but recent improvements in the technics of ex*traction have produced preparations con*taining less than 50 per cent of impurities Such material possesses an activity of 500 to 800 Oxford units per milligram Pure crystalline penicillin has been found to assay about 1600 units per milligram

Pharmacology —An understanding of the pharmacologic properties of penicillin is essential if one is to achieve a maximal therapeutic effect Penicillin is inactivated by the hydrochloric acid of the gastric juice following oral administration and by the action of certain intestinal bacteria notably *Escherichia coli* after rectal instillation Its enteral administration is therefore not effective

Penicillin is readily absorbed following either intramuscular or intravenous injection but in persons with normal renal function it is rapidly excreted in the urine Consequently injections must be repeated at intervals of not more than three hours if an effective concentration is to be maintained in the tissues throughout the course of treatment Continuous intravenous drip is another satisfactory method of ensuring a constant level of penicillin in the tissues

After intramuscular or intravenous injection penicillin does not pass into the cerebrospinal fluid or the various serous spaces of the body in significant concentrations It is essential therefore that penicillin be introduced directly into the infected cavity in the treatment of meningitis empyema and infections of the joints Absorption from these sites is slow so that penicillin need be introduced locally in this manner only once or twice daily

The local use of penicillin is also of value

* The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council

come negative within three to six weeks In late syphilis with cutaneous or central nervous system manifestations dramatic resolution of the signs of the local infection have been observed after treatment with penicillin It should be emphasized that the use of penicillin in the treatment of syphilis is still in the stage of preliminary investigation and that no information is yet available as to the permanency of the improvement thus effected the optimal schedule of treatment or the possible hazards of penicillin therapy especially in patients with syphilitic aortitis

Bacterial endocarditis is a disease notoriously resistant to all forms of therapy Early experiences with the use of relatively small doses of penicillin were almost uniformly discouraging More recently the administration of 200 000 to 300 000 units a day for periods of two to three weeks has produced improvement in a considerable percentage of cases However a marked tendency to relapse within a few days to a few weeks after the discontinuation of treatment has been observed in the cases that have shown temporary improvement Observations conducted over a long period of time will be necessary before any final conclusions can be drawn regarding the possibility of permanently arresting this infection

Of the forms of bacterial endocarditis that have been treated that caused by *Streptococcus viridans* has responded best Staphylococcic bacterial endocarditis with a few striking exceptions has not responded well to even massive doses of penicillin Bacterial endocarditis caused by the pneumococcus appears to occupy an intermediate position

In a few cases patients with *actinomycosis* have shown marked improvement after the administration of penicillin Relapses are frequent and several strains of actinomyces have been encountered that show a marked resistance to the action of penicillin

In mixed infections in which the predominating organism is of the gram negative flora penicillin has proved to be of questionable value In this group are included the complications following ruptured appendix liver abscesses and urinary tract infections

Penicillin has been found totally ineffective in a large group of miscellaneous diseases of known and unknown etiology, so that its use in these conditions is unjustified These conditions are listed below

1 *All gram-negative bacillary infections* typhoid and paratyphoid fever dysentery *Escherichia coli* infections *Hemophilus influenzae* infections *Bacillus proteus* infections *Bacillus pyocyaneus* infections *Brucella melitensis* (undulant fever) tularemia *Friedlander bacillus* infections
2 Tuberculosis
3 Toxoplasmosis
4 Histoplasmosis
5 Acute rheumatic fever
6 Lupus erythematosus diffuse
7 Infectious mononucleosis
8 Pemphigus
9 Hodgkin s disease
10 Acute and chronic leukemia
11 Ulcerative colitis
12 Coccidioidomycosis
13 Malaria
14 Poliomyelitis
15 Blastomycosis
16 Nonspecific iritis and uveitis
17 Moniliasis

Dosage —The dosage of penicillin varies from one patient to another depending on the type and severity of the infection Experience has shown that recovery has occurred in many serious infections following the administration of 40 000 to 50 000 Oxford units a day In other cases 100 000 to 200 000 units or even larger doses are necessary The objective in every case is to bring the infection under control as quickly as possible The following recommendations are made at the present time with a full realization that revisions may be necessary as experience accumulates

1 *In serious infections with or without bacteremia* an initial dose of 15 000 or 20 000 Oxford units intravenously or intramuscularly with continuing dosage as follows

a) A constant intravenous infusion of penicillin in normal saline or 5 per cent glucose solution at a rate of 2000 to 5000 Oxford units an hour Occasionally the dosage may have to be increased to 10 000 units an hour for the first few days
b) When a constant intravenous infusion is not desirable 10 000 to 25 000 units injected intramuscularly every three hours
c) After the temperature has been normal for two to five days omission of penicillin and careful following of the course of the disease

essary to effect recovery In many situations this agent must be considered only as an adjunct to surgery and not as a substitute for surgical procedures of established value Experience has shown however that penicillin frequently renders the surgeon s task easier by improving the patient's general condition allowing the surgeon to select the optimum time for operation, decreasing the extent of the surgery necessary and greatly shortening the recovery period

Clostridia infections such as gas gangrene and malignant edema are favorably influenced by penicillin, but large doses are necessary The urgent necessity for the administration of antitoxin and for the surgical removal of necrotic and devitalized tissue is not lessened by the use of penicillin

Hemolytic streptococcic infections with bacteremia and all serious local infections caused by the hemolytic streptococcus are best treated with penicillin The response to treatment in acute invasive infections such as cellulitis, erysipelas and puerperal sepsis is frequently dramatic Cases in which the infection has become localized with destruction of tissues and impairment of the blood supply as in empyema peritonitis and meningitis may require more prolonged treatment before recovery is assured

Anaerobic streptococcic infections respond irregularly to the use of penicillin In several cases a striking therapeutic response has been observed, in others penicillin appears to have had no effect on the course of the disease Since it may be effective and since it is known that the sulfonamides are never effective the use of penicillin in all cases of anaerobic streptococcic infections appears to be indicated

Pneumococcic infections of all types are definitely susceptible to penicillin and its use is frequently advisable This is true in all pneumococcic infections in which for any reason the sulfonamides are contraindicated or in which their use would be hazardous It is also true of cases of pneumococcic pneumonia in which there is definite or strongly suggestive evidence that the infecting strain is resistant to the sulfonamides

In *three types* of pneumococcic infections penicillin is definitely the *drug of choice* Before the advent of penicillin pneumococcic bacterial endocarditis was inevitably fatal With its use an occasional recovery has been observed, although in the great majority of cases the outlook is still unfavorable

About 45 per cent of the patients with pneumococcic meningitis treated with penicillin have recovered a result somewhat better than that generally obtained with the sulfonamides In this disease penicillin should be given both intrathecally and intramuscularly or intravenously for ten to fourteen days It also appears advisable to administer the sulfonamides concomitantly, since penicillin injected intrathecally may not reach all regions of the subarachnoid space and the ventricular system in adequate concentration

In pneumococcic empyema it is frequently possible to sterilize the pleural cavity by three or four injections of penicillin directly into the empyema cavity at intervals of twenty four to forty eight hours In about 50 per cent of cases the fluid is resorbed without recourse to surgical drainage

Gonococcic urethritis or cervicitis resistant to the sulfonamides can be effectively treated with penicillin in 98 per cent of cases In addition it seems advisable to treat with penicillin all cases of gonococcic infections complicated by arthritis ophthalmia peritonitis salpingitis, epididymitis and endocarditis Cases in which such complications are present require more prolonged treatment than do those presenting only a simple urethritis or cervicitis

Meningococcic meningitis is best treated by the sulfonamides In cases in which the infection fails to respond to adequate sulfonamide therapy the use of penicillin may effect recovery

There are three important diseases in which penicillin s an effective agent but in which there has not been sufficient time as yet to define its position These are syphilis bacterial endocarditis and actinomycosis

In both *early* and *late syphilis* the use of penicillin is followed by striking changes In primary and secondary syphilis spirochetes disappear as rapidly from the local lesions as they do after the use of the arsenicals while the serologic tests for syphilis usually be-

INDEX

NOTE In this index the expression *vs* has been used to denote differential diagnosis Thus Abscess subphrenic *vs* pleurisy with effusion is the equivalent of Abscess subphrenic, differential diagnosis with pleurisy with effusion

2 *In chronic localized infections* such as osteomyelitis a dosage schedule of 10 000 to 15,000 units injected intramuscularly every three hours is usually effective Treatment should be continued until cultures from the local lesions have been sterile for five to seven days

3 *Sulfonamide resistant gonococcic infections*

a) In uncomplicated urethritis or cervicitis 10 000 units given every three hours intramuscularly or intravenously for ten doses has proved effective It is likely that the same effect can be obtained with the administration of 20 000 units every three hours for five doses The results of treatment should be controlled by culture of the exudate

b) When complications are present treatment for three to five days may be necessary

4 *Empyema* —30 000 to 40 000 units of penicillin dissolved in normal physiologic saline solution should be injected directly into the empyema cavity once or twice daily after the aspiration of whatever pus or fluid is present Treatment should be continued until no organisms can be found on either smear or culture of the exudate

5 *Meningitis* —Penicillin must be administered intrathecally since it does not penetrate the subarachnoid space in appreciable amounts Ten thousand to 15 000 units diluted in physiologic saline solution to a concentration of 5000 units per cc should be injected into the lumbar sac or the cisterna magna once or twice a day Intramuscular or intravenous therapy should be given concomitantly Both parenteral and intrathecal therapy should be continued for several days after apparent recovery

Toxic Reactions —Penicillin has been administered to several thousand patients without causing any serious toxic reactions No deleterious effects on the kidneys liver or hematopoietic system have been observed The reactions that have been observed include pain at the site of intramuscular injection thrombophlebitis at the site of intravenous injection occasionally accompanied by chills and fever and in a few cases diarrhea with or without abdominal cramps One reaction deserves special mention From 2 to 5 per cent of the patients receiving penicillin develop urticaria This phenomenon may occur on the first day of therapy or may not occur until several days after therapy has stopped More commonly, however, it appears between the seventh and fourteenth day of treatment Aside from the discomfort that it causes the patient it does not appear to be serious Frequently it has disappeared after a few days while therapy has been continued Readministration of penicillin at a later time may or may not evoke urticaria

At present there are no known *contraindications* to the use of penicillin in the treatment of susceptible infections

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